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EPN Comments on Carbon Tetrachloride Draft Risk Evaluation
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The Environmental Protection Network (EPN) is an organization comprised of almost 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 insights into regulations and policies proposed by the current administration that have a serious impact on 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 carbon tetrachloride (CCl4) draft risk evaluation during their scheduled February 25-26, 2020, meeting.

CCl4 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. Production and use was to be completely phased out under the Montreal Protocol (MP) and 1990 Clean Air Act (CAA) Amendments. However, only production and use as a non-feedstock were curtailed, and it remains a feedstock component in the manufacture of hydrochlorofluorocarbons (HCFCs), hydrofluorocarbons (HFCs), and hydrofluoroolefins (HFOs), and in the manufacturing of other chlorinated compounds, agricultural products, and petrochemicals. The HCFCs and HFCs have now also been subjected to manufacturing and use control under the MP. EPA has identified information on several other uses that may still exist, including solvents for laboratory uses, degreasing and cleaning, adhesives, sealants, paints, coatings, rubber, cement, and asphalt formulations.

New issues:

1) Legacy Uses

In the 2017 Scoping document, EPA stated, "In the case of carbon tetrachloride, legacy uses and associated legacy disposals will be excluded from the scope of the risk evaluation. EPA is excluding these uses because EPA interprets the mandates under section 6(a)-(b) to conduct risk evaluations and any corresponding risk management to focus on current and prospective uses, rather than reaching back to evaluate the risks associated with legacy uses, associated disposal, and legacy disposal, and interprets the definition of conditions of use in that context" (Page 9), noting that this would be the approach set forth in the risk evaluation process rule. The agency further stated that "As a result of this phase-out and ban, it is highly unlikely that there are any ongoing uses of carbon tetrachloride that could be considered legacy uses, and no such uses have been evaluated" (Page 15).

Multiple challenges to the 2017 Risk Evaluation Rule promulgated by EPA in accordance with the 2016 updates of the Toxic Substances Control Act (TSCA) followed its issuance. A decision in the U.S. Court of Appeals for the Ninth Circuit (Ninth Circuit) was issued in late 2019. While the Court sided with the agency

on the majority of its arguments, it did find that legacy activities should NOT be excluded from the definition of conditions of use and should be analyzed during risk evaluations.

Therefore, in accordance with this ruling, the agency is obligated to revise this draft risk evaluation to incorporate the assessment of any identified legacy uses and then re-issue an expanded and updated assessment for further peer review and public comment, taking into account its previous declaration that "EPA may consider background exposures from legacy use, associated disposal, and legacy disposal as part of an assessment of aggregate exposure or as a tool to evaluate the risk of exposures resulting from non-legacy uses" (Page 13 of Scoping document).

2) <u>Ecological Risk Assessment</u>

EPN has conducted a substantive review of EPA's evaluation of ecorisk and concluded that, in general, it appears to be appropriate, although we question some aspects of EPA's approach.

<u>Exposure:</u> Aquatic environmental exposures appear to be appropriately derived.

EPA modeled industrial discharges to surface water to estimate surface water concentration using Toxics Release Inventory (TRI) and EPA National Pollutant Discharge Elimination System (NPDES) permit Discharge Monitoring Report (DMR) data on the top 10 highest CCl4 releasing facilities. EPA used the Probabilistic Dilution Model (PDM) within E-FAST to estimate annual discharges for the facilities. In estimating a range of conservative surface water concentrations, the 2015 NPDES DMR data reporting CCl4 discharges were used as a high-end range of possible release days (i.e., 20 and 250 days/year), allowing the estimation of conservative CCl4 surface water concentrations (i.e., conservative exposure scenarios). Appendix E presents the first-tier estimate of surface water concentrations.

NOTE: Table 4-2 in the EPA draft reports that "San Diego Sea World facility (CA0107336) was not included in the analysis since the reported level is above permit discharge limits; noncompliance and spills are not in the scope of this risk evaluation." Given the relevance of the 2016 Lautenberg TSCA amendment and Ninth Circuit finding that EPA should no longer be ignoring spills, it might be worthwhile to inquire whether those understandings also apply to NPDES permit discharge limits. Table 4.2 reported zero data from that Sea World source, but those missing data may now be accessible and worth pursuing to incorporate into the EPA risk evaluation for CCl4.

CCl4 is expected to remain in aqueous phase due to its water solubility and low partitioning to organic matter. Consequently, EPA did not further assess exposure to sediment-dwelling aquatic organisms. Therefore, EPA did not find unreasonable environmental risk to aquatic species from the conditions of use for CCl4. Also, exposure to terrestrial organisms was removed from the scope of the evaluation. We believe this exclusion is unjustified under TSCA, which requires a comprehensive assessment of risks to the environment, and recommend that EPA revise the evaluation to address hazards and exposures to terrestrial organisms and make a risk determination for these organisms.

<u>Hazard:</u> Aquatic hazard assessments appear to be appropriately derived.

An acute Concentration of Concern (COC) of 90 μg/L, derived from an experimental amphibian endpoint, is used as the conservative (screening level) hazard level in EPA's risk evaluation for CCl4. The amphibian

chronic COC for CCl4 is 3 µg/L and is used as the lower bound hazard level in the risk evaluation for CCl4. The chronic COC of 7 µg/L, derived from an experimental algal endpoint, is used as the lower-bound hazard level for algal toxicity in this risk evaluation for CCl4.

Again, algae was the most sensitive aquatic species; chronic COC of 7 µg/L appears to be appropriately derived.

One issue raised early in the EPN review dealt with the appropriateness of dealing with algal risk separately from other aquatic species. The EPA draft points out [lines 3096-3100] that previously, algal endpoints were considered together with data from other taxa in the acute and chronic COC calculations. Now, algal endpoints are considered separately from the other taxa and not incorporated into acute or chronic COCs because durations normally considered acute for other species (e.g., 48, 72, or 96 hours) can encompass several generations of algae. A distinct COC is calculated for algal toxicity.

Our understanding is that the approach used in the 2020 EPA draft for assessing CCl4 risk to algae was developed gradually over time. EPA's New Chemicals Program circa 2010 used different values to develop "acute concern concentrations" for fish and algae. That practice was based, in large measure, on the difference in toxicity test designs: Fish testing measures adverse effects (e.g., death, lethargy) to *discrete organisms*. Algal testing is designed to detect changes to growth via changes in biomass (typically inhibition, but may also measure stimulation or lethality) of *populations of algal cells* compared to control populations. This dissimilarity in test design has always challenged attempts by reviewers to normalize results from testing individual organisms against results from testing populations. Comparing results of short-term "acute" tests of individual organisms, e.g., daphnids or fish, with results of short-term "chronic" tests, e.g., algae, conflicts in fundamental ways. For example, algal species used in testing are typically single-celled organisms with life cycles that range from days to years. Fish and aquatic invertebrates used in testing are discrete, multicellular organisms with life cycles that range from weeks to years. When all is said and done, EPN is inclined to accept using the slightly different approach taken by authors of the 2020 EPA draft for treating results from algal testing.

This view recognizes that 72-hour or 96-hour algal testing can be appropriately described as both an acute and a chronic exposure to a test substance because exposure takes place in a relatively short duration, but it also occurs during the reproduction of populations of individual algal cells, and it's those developing and changing cell populations that are measured. The fairly well defined and easily measured endpoint of death in individual organisms, e.g, fish, is quite different from the measuring of inhibition of growth in large populations of photosynthetic algal cells. Those endpoints are clearly quite different.

Risk: The environmental risk evaluation EPA developed in their Jan. 2020 draft appears, for the most part, to be appropriately derived for CCl4.

For environmental risk, EPA used risk quotients (RQ) to compare environmental concentrations to effect levels to characterize the risks to aquatic organisms. Although EPA qualitatively assessed CCl4 exposure from sediments and land-applied biosolids, it is not expected to accumulate in sediments, could be mobile in soil, migrate to water, or volatilize to air. Section 4.1 gives results of the risk characterization, including a table summarizing RQs for acute and chronic risks. EPA determined there were no acute or chronic environmental risks from the TSCA conditions of use of CCl4. EPA used conservative scenarios to demonstrate that, for all sites except one [Dover Chemical Corp] (i.e., acute RQ = 1.4), surface water

concentrations did not exceed acute or chronic COCs (i.e., RQs < 1) for aquatic species. EPA determined this was not an acute aquatic concern because it was a one-time chemical spill in 2014 (see footnote c, Table E-1, draft line 6856). However, following the 2016 TSCA amendments, we do not believe that EPA can ignore RQs above 1 just because they allegedly result from spills. In those amendments, Congress required EPA to look at known, intended, and reasonably foreseen releases from a chemical's conditions of use, which may include spills. The Ninth Circuit has also held that "spills, leaks, and other uncontrolled discharges ... would thus qualify as 'disposals' (and therefore conditions of use)." To reiterate, we therefore don't believe that EPA can ignore RQs above 1 just because they allegedly result from spills.

EPA modeled discharges of CCl4 to surface water to estimate surface water concentrations. The estimated surface water concentrations did not exceed the acute COC for aquatic species for all but one of the sites assessed, where that exceedance was due to a chemical spill. None of the sites analyzed had more than 20 days where the chronic and algal COCs were exceeded.

NOTE: There appears to be a typographical error (Lines 7020, 7023-7025) where it states, "Therefore, the amphibian 9-day lowest LC50 of 0.09 mg/L and LC10 of 0.037023 mg/L were used to derive an acute COC in Appendix Section G.5 and chronic COC in Appendix Section G.6." In reviewing Health and Environmental Research Online (HERO) abstracts (HERO ID 3616521) of the original literature, it appears the median lethal concentration[= LC50]s were reported over the range of 0.90 to 2.83 mg/L for CCl4. Given that 0.90 mg/L is the lowest reported value from that range and used by EPA in developing the acute COC, and that 0.90 mg/L may also be reported as approximately 900 ug/L, the appropriate acute LC50 for the most sensitive species [Pickerel Frog] is 900 ug/L. That value divided by an assessment factor of 10 results in an acute COC of 90 ug/L, which seems to be appropriately used in the rest of the EPA draft report on CCl4.Happily, in G.5 Hazard Estimation for Acute Exposure Durations on lines 7066-7067, the acute COC appears to use the correct value, i.e., the "acute COC = (0.9mg/L)/(AF of 10) = 0.09mg/L x 1,000 = 90μg/L or 90ppb."

3) *De Minimis* and Exclusion of Consumer Products

In the 2018 CCl4 Problem Formulation document and in the draft Risk Evaluation document currently undergoing public comment and peer review, EPA states that it has removed all consumer conditions of use from the evaluation. The rationale for this exclusion is that these uses "would present only *de minimis* exposure or otherwise insignificant risk." The Problem Formulation document states: "Therefore, as a general matter, EPA does not expect to analyze consumer exposures or associated hazards in the risk evaluation for carbon tetrachloride, and accordingly the initial conceptual model for consumer activities and uses presented in the Scope of the Risk Evaluation for Carbon Tetrachloride (U.S. EPA, 2017e) does not appear in this problem formulation document" (Page 21).

EPN objects to this decision. The agency has neither provided its definition or interpretation of "*de minimis"* or "insignificant risk" nor presented any criteria by which one can determine if a condition of use, in fact, represents *de minimis* or insignificant risk. CCl4 is known to be released from consumer products and several products known to contain CCl4 remain in use. As an example, CCl4 has been shown to be released into indoor air from household bleach (Odabaşı, M. (2008), *Halogenated volatile organic compounds from the use of chlorine-bleach-containing household products*, Environmental Science & Technology, 42 5, 1445-51). It has also consistently been measured in indoor air at higher levels than in outdoor air (ATSDR Tox Profile at 189), suggesting releases from products used inside buildings. Given its volatility and known carcinogenicity,

releases from consumer products may present significant risks. We recommend against excluding consumer products and urge EPA to conduct the same analysis of their risks that it is performing for other conditions of use. EPN also recommends that EPA evaluate the cumulative effect of all *de minimis* conditions of use that are expected to co-occur in order to evaluate their combined effect on risk.

Continuing Issues:

4) Systematic Review

EPN has commented before, and feels compelled to repeat it once again—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.

While the agency claims that it is making/has made arrangements for the National Academies of Sciences (NAS) to review and comment on the draft guidance document entitled "Application of Systematic Review in TSCA Risk Evaluations," this review is not likely to be completed before the CCl4 evaluation and those for the other nine chemicals in the first batch of 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.

5) Aggregate Risk Assessment: Combining All Relevant Routes of Exposure Within a Condition of Use and Across Exposure Scenarios Addressed by Other Statutes

The CCl4 draft risk evaluation presents risk assessments and risk determinations for acute and chronic inhalation and dermal exposures to worker and occupational non-user (ONU) populations under a variety of conditions of use. As EPA notes once again in this draft risk evaluation, it is required to describe whether aggregate or sentinel exposures under the conditions of use were considered and the basis for their consideration. (The agency defines aggregate exposure as "the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways.")

While the agency states that they must describe whether or not they have considered aggregate exposures in their assessments, they, as usual, have not conducted such an assessment for CCl4 or made their unreasonable risk findings based upon combined exposures, either for a specific condition of use or with consideration of exposures from non-TSCA-related scenarios.

As seen in all of the scenarios evaluated for CCl4, and as EPA observes in the draft evaluation, exposure via the inhalation and dermal routes will most likely be occurring simultaneously. This observation notwithstanding, the agency ignores the reality of concurrent exposure by different routes and evaluates the exposures to inhalation and dermal contact separately. Thus, the draft evaluation does not determine the risks of the acute or chronic scenarios with a composite Benchmark Margin of Exposure (MOE). EPA argues that there is, in reality, little potential for dermal exposure because workers will wear gloves, but it provides no data to support this assumption and, in fact, states that it has no basis to determine the frequency of glove use.

Some extra effort would be required to do an aggregate assessment in the case of the acute exposure scenarios, given that different studies and different endpoints (one study in humans—neurotoxicity, the

other in guinea pigs—liver) were used to derive points of departure (PODs) for each acute route of exposure. In addition to doing the necessary math to convert the administered or internal dose for each route to the same metric, a decision would have to be made as to what the appropriate Benchmark MOE would be.

EPA's current assessment shows no MOE exceedances for acute inhalation exposure to the unprotected (that is, no personal protective equipment (PPE)) worker or ONU under any condition of use. Even if the intra-human uncertainty factor of 10X were enlarged to 12 or 15 (the rationale for this modification is presented below in Item #6) to reflect a greater-than-default variability in the human, and increasing the Benchmark MOE from 10 to 12 or 15, there would still be no exceedances.

The same situation exists with regard to acute dermal exposure scenarios. EPA's current assessment shows no MOE exceedances for acute dermal exposure to the unprotected (no PPE) worker or ONU under any condition of use. Even if the intra-human uncertainty factor of 10X were increased to 12 to 15 (a reasonable upper-bound enhancement, in our view) to reflect a greater-than-default variability in the human, and increasing the Benchmark MOE from 100 to 120 or 150, there would still be no exceedances.

What remains unknown, however, is whether or not the conclusions would be the same if an aggregate exposure and risk assessment were conducted, implementing the recommendations for modifications to the MOEs.

Based upon the outcome of the acute exposure assessments, EPN would not, *at this time*, recommend that CCl4 be subjected to the two-step regulatory process that EPN and others have recommended for 1-Bromochloropropane (1-BP) and methylene chloride (MC). This will be revisited if/when the risk evaluation is modified in accordance with the EPN recommendations.

Aggregation can be done relatively easily for the chronic exposure scenarios. The same study and set of endpoints are used for both the inhalation and dermal assessments, as the latter is extrapolated from the same data used for the inhalation assessment. This is true for both the non-cancer (endpoint = fatty liver) and cancer (endpoint = increased tumor incidences [liver and pheochromocytoma]) assessments.

The lack of aggregation leads to an underestimate of exposure and risk and, potentially, an incorrect declaration of "no unreasonable risk" when one actually exists. This situation is further compounded by EPA's refusal to consider concomitant exposures in media/scenarios covered by regulatory measures under other statutes. Examples of exposures excluded from the risk evaluations include known air emissions, drinking water-related exposures and waste-related exposures. CCl4 air emissions are significant due to its high volatility; measured ambient levels in air exceed the cancer benchmarks according to EPA's Integrated Risk Information System assessment. The same is true of drinking water levels, which in many cases exceed a one in one million cancer risk as well.

6) <u>Impacts on Ozone Depletion and Climate Change</u>

Of particular importance is CCl4's impact on ozone depletion and climate change. CCl4 degrades slowly in the atmosphere and is a significant contributor to stratospheric ozone depletion. Although CCl4's emissive uses are controlled and practically banned by the MP, previous work estimated ongoing emissions of 35 Gg $year^{-1}$ of CCl4 into the atmosphere from observation-based methods, in stark contrast to emissions

estimates of 3 (0–8) Gg year^{-1} from reported numbers to United Nations Environment Programme under the MP.[1] Emissions of CCl4 derived from inverse modeling based on National Oceanic and Atmospheric Administration's air sampling network are nearly two orders of magnitude greater than those reported in EPA's TRI. The emission distribution is more consistent with ongoing industrial activity than with closed disposal sites. Global emissions of CCl4 are substantial when compared with other ozone-depleting substances, accounting for 11-17% of all ozone depletion-weighted emissions.[2] Stratospheric ozone filters out 90% of the UV-B rays and 50% of the UV-A rays from the sun, thus providing considerable protection against sunburn and skin cancer.[3]

CCl4 possesses a global warming potential 1,730 times that of carbon dioxide (CO_2).[4] This means that the emissions of CCl4 of nearly nine million pounds per year is equivalent to nearly six million metric tons of CO_2, which makes it higher than the emissions of most coal-fired power plants or the equivalent to the CO_2 emissions of 1.5 million cars.[5]

These reports demonstrate once again the fallacy of EPA's dismissing from consideration in its risk evaluation releases and exposures that are controlled under an existing statutory authority or regulation. The CCl4 draft risk evaluation also omits any assessment of risks to the general population or the environment. EPA's exclusion of all environmental exposure pathways defeats the TSCA goal of providing a comprehensive assessment of a chemical's risk to human health and the environment.

Bottom line: Exposure assessments and unreasonable risk determinations for conditions of use subject to risk evaluation under the TSCA Existing Chemicals program should aggregate exposures from all relevant routes/pathways of exposure regardless of statutory relationships. The CCl4 risk evaluation should re-evaluate the health and environmental toxicity impacts these releases may cause. In addition, the risk evaluation should address the risks that these CCl4 emissions contribute to climate change and ozone depletion. To do otherwise blatantly underestimates potential risk and endangers the public health and the environment. The agency's current approach is bad science and bad policy.

7) Adequacy of Databases for Assessment and Derivation of PODs, Reference Values ,and Benchmark MOEs

As with all chemicals selected for review in the Existing Chemicals Risk Evaluation program, EPN is concerned about the adequacy of the database available to assess CCl4's hazard potential to human health and to characterize the relevant exposure profiles. We have previously articulated our views on what constitutes a minimum database with which to estimate high-confidence PODs/reference values/MOEs, most recently in comments submitted on MC.

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[1] Sherry D *et al.* Current sources of CCl4 in our atmosphere (25 January 2018) Env Research Letters, vol 13, no. 2

[2] Hu L *et al.* Continued emissions of CCl4 from the US nearly two years after its phaseout for dispersive uses (March 1, 2016) PNAS, vol. 113, no. 11

[3] sciencing.com/percent-uv-ozone-absorb-20509.html

[4] [4]EPA, Ozone Depleting Substances, https://www.epa.gov/ozone-layer-protection/ozone-depleting-substances

[5] According to EPA, a typical passenger vehicle emits about 4.6 metric tons of carbon dioxide per year. https://www.epa.gov/greenvehicles/greenhouse-gas-emissions-typical-passenger-vehicle

This draft risk evaluation includes the assessment of risk to workers and ONUs from acute and chronic inhalation and dermal exposures. However, neither pregnant women nor male workers considering a family nor the general population, which also includes infants and young children, have been specifically addressed. This becomes particularly important once the risk evaluation is updated to include the analysis of legacy consumer conditions of use.

EPA identified the following endpoints of concern related to CCl4 exposure in its hazard assessment: acute toxicity, neurotoxicity, liver and kidney toxicity, reproductive/developmental toxicity, and carcinogenicity. **We would argue that dermal irritation and sensitization should also be listed as likely endpoints of concern. However, since there are no studies that evaluate the potential for reproductive effects, this endpoint should NOT be cited on EPA's list.**

What, then, would constitute a database adequate for assessing hazard to workers and ONUs with regard to the identified toxicity endpoints of concern for determination of credible PODs, reference values, and Benchmark MOEs? Databases, historically, have been heavily dependent upon whole animal studies in the absence of adequate human data. In this instance, there is a body of literature on human exposure, both controlled exposure and epidemiologic studies, that do provide credible information from which to derive *acute* PODs and reference values. The database also contains a series of short-term *in vitro* and *in vivo* genotoxicity studies, but no others focused on the characterization of mode(s) of action (MOA) for any of the observed toxicity endpoints, including carcinogenicity. Furthermore, there are no studies, human or animal, that focus on characterizing the potential for adverse effects on reproduction or neurodevelopment.

As EPN has asserted in the past, absent fulsome observations in humans with useful dose-response characteristics, the following types of information are needed in order to conduct a credible hazard assessment and derive useful PODs and appropriate Benchmark MOEs, without having to incorporate an uncertainty factor to accommodate for database deficiencies:

a) Studies that would illuminate the potential for general systemic toxicity over exposure duration(s) commensurate with that/those of the actual exposure scenario(s) under evaluation or, if long term, 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). In this draft risk evaluation, both acute and long-term exposure scenarios are being evaluated;
b) For chronic exposures, studies that would adequately test for carcinogenic potential by the relevant route(s) of exposure or that could be extrapolated to those routes of exposure;
c) For both acute and chronic exposures, at least one developmental toxicity study;
d) For both short-term and chronic exposures, a one- or two-generation reproductive toxicity study and;
e) If nervous system effects have been observed in exposed humans or animals over a short-term or chronic time frame, a more systematic evaluation of neurotoxicity and developmental neurotoxicity, since the worker and population includes women of childbearing age. Once the risk evaluation is updated to include analyses of any remaining legacy consumer conditions of use, infants and young children become a subpopulation of concern.

i) *Adequacy of Databases for Assessing the Acute Inhalation and Dermal Exposure Scenarios*

EPA notes that "Human case reports following acute exposures identify liver as a primary target organ of toxicity and the kidney as an additional primary target organ of toxicity. Neurotoxicity indicated as central nervous system (CNS) depression is another primary effect of carbon tetrachloride in humans following acute exposures, with examples of neurotoxic effects including drowsiness, headache, dizziness, weakness, coma, and seizures. Gastrointestinal symptoms such as nausea and vomiting, diarrhea and abdominal pain are considered another initial acute effect" (U.S. EPA, 2010; ATSDR, 2005; Page 101).

EPA has derived acute inhalation PODs of 360 mg/m^3 for an 8-hr exposure duration and 310 mg/m^3 for a 12-hr exposure duration, based upon the observation of temporarily disabling neurotoxic effects in humans. One 10X uncertainty factor was employed to accommodate for within-human variability, and a Benchmark MOE of 10 was established.

EPA has derived an acute dermal exposure POD of 2,750 mg/kg-d, based upon acute dermal studies in guinea pigs, which revealed histopathological changes in the liver. Two 10X uncertainty factors were applied to account for interspecies and intra-human variability, and a Benchmark MOE of 100 was established.

EPA explicitly asserts that the inhalation assessment is protective of heavy alcohol users and is silent on that point with regard to the dermal assessment, although one might interpret equivalency. It is fairly well understood that CCl4 metabolite interaction with CYP450 enzymes, particularly in the liver, is a key event in the toxicity of this compound and that alcohol consumption, among other factors, plays a role in the nature and magnitude of any adverse response.

EPN would be generally supportive of the acute exposure assessments *IF* the agency could provide substantive documentation that the 10-fold intra-human uncertainty factor was, in fact, sufficient to accommodate for the impact of heavy alcohol use—a not-unexpected lifestyle practice of some among the populations being assessed in this risk evaluation. Without such documentation, one might consider it appropriate to expand the UF_H to 12-15 and the Benchmark MOE to 12-15 from 10.

EPN sees no need for a database uncertainty factor to be employed in the acute exposure assessments.

ii) *Adequacy of Databases for Assessing the Chronic Inhalation and Dermal Exposure Scenarios:*

In the case of CCl4, there exists a database comprised of a number of controlled human exposure and epidemiology studies as well as animal and some *in vitro* studies, *but they do not adequately cover the full range of endpoints required to exclude a database deficiency uncertainty factor.* As noted above, there are no studies that evaluate the potential for reproductive effects, a significant deficiency, given that men and women of active reproductive age are likely to be members of both the worker and ONU populations. Furthermore, by the agency's own admission, the available genotoxicity studies are not well-tailored for this chemical (Page 287-288 of the draft risk evaluation). This is particularly important in this case because the chemical clearly exhibits carcinogenic potential at multiple tissue sites in multiple animal species. Significant effort has been directed to characterizing the MOA/adverse outcome pathways (AOPs) at these sites, with agreement on this point not yet realized. Some additional work is needed, which will also lead to consensus on the appropriate choice(s) for dose response assessment. And thirdly, the chemical is clearly neurotoxic; this endpoint serves as the basis for the derivation of the acute inhalation exposure POD and Benchmark MOE.

Bottom line:

a) **A database deficiency uncertainty factor >1X (at least 3X) should be incorporated when deriving the chronic non-cancer Benchmark MOE, raising it from the current agency choice of 30 to at least 100. And, as for the acute exposure scenarios, the agency must provide adequate documentation that the 10X intra-human uncertainty factor adequately covers the special populations it acknowledges. Without such documentation, one might consider it appropriate to expand the range of UF_H to 12-15. The resulting non-cancer chronic Benchmark MOE, which would encompass the uncertainties related to interspecies toxicodynamic and intra-human variability and database deficiencies, would increase from 30 to 120 or 150 (UF_A x UF_H x UF_D = Benchmark MOE: 3.16 x 12 x 3.16 = 120 or 3.16 x 15 x 3.16 = 150).**
b) **The agency should use its enhanced testing authority in the "new" TSCA to require submission of the studies noted above (reproduction, genotoxicity, developmental neurotoxicity, and others relevant to MOA/AOP characterization).**

8) <u>Worker and ONU Exposure and Risk</u>

EPN continues to be concerned about the agency's approach for determining unreasonable risk to workers (and others). It clearly underestimates risk by assuming workers will use PPE for the entire duration of the work activity throughout their careers, even when such equipment is not required, provided or used. EPA discounts the risks by assuming constant use of PPE (e.g., respirators and/or gloves). We would argue that while EPA appropriately assesses and characterizes worker risk with and without the use of PPE, it should make its unreasonable risk determinations based upon the "no PPE" scenarios. Lacking the guarantee of consistent use of PPE, EPA should focus its regulatory options on mitigating risk to the unprotected individual, whether it be a worker or member of a different subpopulation.

This draft risk evaluation employs the same old misguided approach. The agency has concluded that "For all applicable conditions of use, acute and chronic inhalation and dermal exposure scenarios resulted in calculated MOEs and cancer risk levels that did not indicate risk *with expected PPE"* (emphasis added)(Page 176).

On the other hand, EPA did identify a number of conditions of use in which ONUs are subject to unreasonable risk situations, and, hopefully, will proceed with measures to mitigate these risks. Appropriately, the findings were made under the assumption that PPE is not used by this subpopulation.

Bottom line: In any case, EPN believes that EPA should re-evaluate all conditions of use for both the worker and ONU populations, implementing the modifications to the exposure assessments, PODs, and Benchmark MOEs recommended above. It is expected that some number of scenarios would flip from a declaration of "no unreasonable risk" to one of "an indication of unreasonable risk," increasing the number of scenarios requiring risk mitigation.