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EPN Comments on the Manufacturer's Request for Risk Evaluation for the Chemical Category for Octahydro-Tetramethyl-Naphthalenyl-Ethanone (OTNE) Isomers and Points to Consider as EPA Re-examines How It Intends to Implement the Provisions of the Amended TSCA

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The Environmental Protection Network (EPN) is an organization of over 550 U.S. Environmental Protection Agency (EPA) alumni volunteering their time to protect the integrity of EPA, human health, and the environment.

These comments are divided into two sections:

1. Comments specific to the Chemical Category for Octahydro-tetramethyl-naphthalenyl-ethanone (OTNE) Manufacturer Request for Risk Evaluation Under the Toxic Substances Control Act (TSCA) and
2. Points to consider as the agency re-examines implementation of the provisions of the amended TSCA.

1. The Chemical Category for OTNE Manufacturer Request for Risk Evaluation Under TSCA

A. Comments Specific to the OTNE Consortium's Manufacturer's Request Letter

Data availability and adequacy

The risk evaluation for the OTNE category is likely to be highly dependent upon studies sponsored by OTNE Consortium member companies. The Consortium noted in the request letter that "Study reports cited in the Reference section of the Appendices that are not publicly available are also included with this risk evaluation request." These study reports "include information regarding physicochemical properties, conditions of use, environmental fate, engineering, and exposure, as well as human health and environmental hazards." Unfortunately, this list of information represents some, but not all, of the key domains required to conduct a robust risk evaluation (see Appendix VI of the request letter).

On this latter point of "some, but not all…" there is no list available to the public, at this time, of all studies available for review and use in the risk evaluation (that is, both company-sponsored and those published in the open and grey literature identified via a credible systematic review process). EPA should already have a systematic review of literature identification, selection and screening for quality underway, with data gaps being identified and steps being taken to fill them BEFORE the clock begins ticking on the risk evaluation.

At this time, since a comprehensive list of candidate studies is not available, EPN cannot agree with EPA's declaration in the February 19, 2021 Federal Register notice that "EPA has all the information needed to conduct such risk evaluation on the conditions of use that were the subject of the request;' and "All other criteria and requirements of 40 CFR 702.37 have been met." The

agency cannot limit the risk evaluation to just the two conditions of use (COUs) that the Consortium asked to be assessed, as TSCA obligates the agency to evaluate ALL relevant COUs, not just those included in a manufacturer's request. In other words, EPA must address all of those circumstances "under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of," both current and legacy.

It is clear from the agency's "Possible Conditions of Use….." document that more COUs exist that also must be evaluated. Additional COUs likely will be identified during the public comment period. These, too, must be added to the list for evaluation.

A quick scan of PubMed reveals that there are a number of papers on OTNE available in the open literature. If many of these papers are reviews of data from the same studies that are listed in Appendix VI, this risk evaluation will be highly dependent upon studies sponsored by OTNE Consortium member companies.

Regarding human health, what can be said about data adequacy at this point in time, given the virtual total dependence upon Appendix VI as the data source? For purposes of discussion, it will be assumed that all of the listed studies will be deemed acceptable, although a final judgment on this must await independent analysis of the detailed study reports.

It is clear that several studies are missing, which may be important to the assessment of human health based upon the exposure conditions of the COUs to be evaluated. EPA has documented that adequate data must be available for 13 areas in order to support a robust human health hazard assessment in a risk evaluation. They are these: acute toxicity; irritation/corrosion; dermal sensitization; respiratory sensitization; reproductive toxicity; developmental toxicity, genetic toxicity; repeated dose toxicity; carcinogenicity; immunotoxicity; neurotoxicity including developmental; toxicokinetics; and epidemiological and/or biomonitoring studies. The number and design of some of these study types may vary, depending upon the route(s) and durations of exposure associated with the COUs. Others may be "triggered" only after observations are made in other studies.

In this case, while it is expected that the predominant route of exposure to OTNE would be dermal, exposure via the oral and inhalation routes may also occur under certain circumstances. While acute oral and dermal toxicity studies have been conducted, an *acute inhalation study* has not. [Note: The European Chemicals Agency (ECHA) granted a waiver for this study under the REACH regulatory program with the justification being "Other," not otherwise explained. However, the decision could have been based upon the fact that the LD_{50}s in the oral and dermal studies both exceeded 5000 mg/kg, a dose level far in excess of any possible human exposure, and one would expect similar results for the inhalation route].

The potential for dermal irritation and sensitization has been tested; *respiratory sensitization* has not. Purportedly, guideline-compliant reproductive and developmental toxicity studies have been conducted by the oral route; route-to-route extrapolation may be warranted to understand dermal and/or inhalation hazard potential. A trio of first-round genotoxicity tests have been conducted,

purportedly consistent with the Organisation for Economic Co-operation and Development guidelines.

One area impacted by incomplete information is toxicokinetics. While uptake, distribution and excretion, as measured by radioactivity, were determined in rats by the oral and dermal routes, no metabolites were identified. Identification and quantification of key metabolites are necessary if the risk evaluation would benefit from the use of physiologically-based pharmacokinetic models to assist in route-to-route and/or cross-species extrapolation rather than requiring additional high-resource, time-consuming animal studies.

A third example of missing information is an examination of the potential for chronic toxicity and carcinogenicity, particularly in light of effects observed in a 13-week dermal study in rats (e.g., skin hyperplasia) and mice (e.g., reproductive system) (NTP, 2016)[1]. Some of the COUs on EPA's expanded list of possible COUs can lead to longer-term exposures and, therefore, require relevant duration of exposure studies to determine the potential for risk.

Also, concern about the potential to induce immunotoxicity has increased substantially in recent years, as we have learned more about the role the immune system plays in both normal and pathological functions of many biological systems. Thus, evaluation of this endpoint has taken on a more prominent role and should be studied in this case.

The agency may wish to require screening for potential reproductive effects, using the Endocrine Disruptor Screening Program Tier 1 screening battery in order to understand their mode(s) of action, given that the National Toxicology Program (NTP) reported that OTNE exhibited the potential to be a reproductive toxicant in male and female mice[1]. Following dermal exposure, treated male mice were shown to have decreased sperm counts and motility; female mice were observed with increased cycle length and extended estrus when compared with untreated controls.

Turning to an analysis of the adequacy of submittedenvironmental testing, again pending a more detailed review of the full and final results of thestudies listed in Appendix VI, and confirming that all testing methods, protocols, and conduct of actual testing are fully validated in accordance with relevant published protocols, guidelines, and good laboratory practices, we think the submitted data are sufficient to assess the environmental hazards and risks posed by OTNE (Octahydro-tetramethyl-naphthalenyl-ethanone as a chemical category).

There are some issues of concern which, hopefully, can be resolved or assuaged following an in-depth review of the studies. There appears to be a discrepancy between one screening study showing OTNE is not readily biodegradable and other studies showing considerable degradation. Also, we would prefer to see results from environmental effects testing conducted over longer durations (e.g., 96 hours for algal and fish acute testing, as opposed to 72 hours).

[1] National Toxicology Program, 2016. NTP Technical Report on the Toxicity Studies of Octahydro-tetramethyl-naphthalenyl-ethanone (OTNE) Administered Dermally to F344/NTac Rats and B6C3F1/N Mice. Toxicity Report 92. National Toxicology Program. Public Health Service U.S. Department of Health and Human Services. Research Triangle Park, North Carolina, USA

We also would prefer to see toxicity testing designs where test solutions are expressed as measured concentrations of toxicant in dilution water, and where toxicant concentrations are measured at reliable intervals when using flow-through testing designs; or in static renewal of test solutions, where fresh and spent test solutions are measured, both before and after testing solutions are renewed, throughout the test duration. This is a particular concern where a test material such as OTNE is known to have low water solubility and is, thus, prone to sorb onto soils and sediments. Tests conducted using nominal concentrations, where test materials are known to be unstable in test solutions, often understate effect concentrations and, consequently, yield misleadingly low toxicity levels.

For similar reasons, we also would prefer to see water quality parameters, (e.g., hardness, dissolved oxygen, total organic matter, total suspended solids) measured and reported for both dilution water and all test solutions in order to more realistically determine how much exposure the test organisms actually had to the test substance.

Finally, another, and somewhat puzzling, situation exists as to the nature of the company-sponsored studies—and, that is, the composition of the test material used in the studies. The Consortium letter makes a case for the four isomers being inseparable, and being "manufactured, imported, and processed as a single chemical product." It is not completely clear if the ratio of the isomers differs in different products and COUs. However, the letter also says that "Test reports may specify the four isomers as the test substance or only a representative isomer." This statement is apparently not true for any of the company-sponsored studies listed in Appendix VI that are components of the REACH dossier. In fact, the dossier notes that all of the company-funded studies were conducted with only three of the isomers in this "inseparable" four-isomer mixture. The test material in all submitted company studies is documented as Constituent #1: Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-(CAS# 54464-57-2); Constituent #2: Ethanone, 1- 1,2,3,4,6,7,8,8 aoctahydro-2,3,8,8-tetramethyl-2-naphthalenyl)- (CAS # 68155-67-9); and Constituent #3: Ethanone, 1-(1,2,3,5,6,7,8,8 aoctahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-(CAS# 68155-66-8), but *never* the fourth Isomer: Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,5,5-tetramethyl-2-naphthalenyl)-(CAS #54464-59-4). This is unlike the 2016 NTP study which employed a mixture of all four isomers. Since there were no company-sponsored studies testing the individual isomers listed in Appendix VI, it is difficult to determine if this exclusion makes any difference in the establishment and definition of the toxicity profile for OTNE.

The request letter also notes that the studies sponsored by two of the Consortium's companies are their property and considered proprietary in an unredacted form. The letter also says that each company has submitted their studies to the agency in a manner that can be shared in the public docket, which should provide commenters and peer reviewers adequate opportunity to assess the data and the quality of the studies.

Sponsors cannot claim health and safety data as Confidential Business Information (CBI). There will be an expectation that all of the raw data from all of the company-sponsored studies in all of the relevant information domains will be available for independent review and analysis. Study summaries posted on the ECHA REACH dossier website are not adequate or appropriate substitutes for the full study reports. EPA had a rude awakening on this point during the early

stages of drafting the risk evaluation for Pigment Violet 29 (PV29). We trust that the agency will not repeat that debacle.

Potentially-exposed and susceptible populations

The amended TSCA requires that the agency consider, identify, assess and eliminate any unreasonable risk a chemical presents or may present to "potentially exposed or susceptible subpopulations" under all conditions of use included in a risk evaluation.

The Consortium's request letter notes that, in this instance, the "potentially exposed or susceptible subpopulations are expected to include infants, children, pregnant women, workers, and the elderly, given the potential for use of OTNE as a fragrance in consumer products such as bath and shower products, personal care products, and laundry products such as fabric softeners and detergents."

Based upon this acknowledgement of potentially exposed or susceptible subpopulations, readers and reviewers of the OTNE risk evaluation will expect to see robust age- and status-specific assessments for each of these (and, perhaps other, subgroups) for each relevant COU, signaling an improvement over the uneven, often inadequate, assessments presented in the risk evaluations for the first ten chemicals.

The agency should add at least one other subpopulation for evaluation—those who suffer irritation or allergic reactions when exposed to fragrances.

According to the American Academy of Dermatology, fragrances are considered the leading cause of cosmetic contact dermatitis. As a health problem, this sensitivity alone affects more than two million people in the U.S. and studies suggest that sensitivity is on the rise (https://www.webmd.com/allergies/features/fragrance-allergies-a-sensory-assault#1). Other health consequences such as asthma attacks, headaches, and respiratory irritation have been reported[2], although some investigators assert that untoward health effects arising from fragrance inhalation are uncommon and their causation remains to be identified[3].

B. Comments Specific to the EPA Document entitled *Possible Conditions of Use (COU) Tables for Octahydro-Tetramethyl-Naphthalenyl-Ethanone Chemical Category ("OTNE")*

The Consortium letter cites correspondence from the then-Office of Pollution Prevention and Toxics (OPPT) Office Director Jeffery Morris, in which EPA agrees to treat the four isomers of OTNE as a category of chemical substances and to prepare a single risk evaluation.

Given that OTNE "is identified as a category of chemical substances consisting of *four inseparable individual isomers*" [emphasis added] (Page 1, OTNE Consortium request letter), "the four isomers

[2] S. M. Caress and A. C. Steinemann. 2009. Asthma and chemical hypersensitivity: prevalence, etiology, and age of onset. Toxicol Ind Health Feb;25(1):71-8.

[3] D. A. Basketter, J. Huggard , and I. Kimber.2019. Fragrance inhalation and adverse health effects: The question of causation. Regul Toxicol Pharmacol Jun;104:151-156. doi: 10.1016/j.yrtph.2019.03.011. Epub 2019 Mar 21.

in OTNE are *manufactured together* [emphasis added], are very similar in molecular structure, in physicochemical and biological properties, in use, and in mode of entrance into the human body and the environment"(Page 2, OTNE Consortium request letter) and "[s]ince OTNE is *an inseparable mixture*"[emphasis added] (Page 16, OTNE Consortium request letter), why, then, are COUs listed in separate tables for each of the four isomers (pages 3-6)? It would seem more appropriate to have a single, all-inclusive table, covering the chemical category and all of its attendant COUs, unless one can show that the isomers are teased apart for any of the COUs, a situation that is not being argued—rather, quite the contrary.

2. Points to Consider as the Agency Re-examines Implementation of the Provisions of the Amended TSCA.

While the February 19, 2021, Federal Register notice invites the stakeholder community to provide feedback to the agency on any and all aspects of implementation of the amended TSCA going forward, EPN's comments will be centered on issues related to the Existing Chemicals Review program at this time. They reflect a compilation of our thoughts on aspects of the review program that EPN has identified during its reviews of agency actions taken—or not taken—during the first four years of implementation of the three-steps process (Prioritization, Risk Evaluation and Risk Management) that, in our view, represent missing, misapplied, or misguided execution of agency-consensus risk assessment principles, science and regulatory policy, timely risk management actions, and other choices. We offer some points to consider as the agency seeks to remedy these flaws.

A. Prioritization

On February 26, 2021, EPN sent a letter to the EPA Principal Deputy Assistant Administrator for Chemical Safety and Pollution Prevention expressing concern that the agency has not effectively utilized the expanded authority granted by Congress under Section 4 of the amended TSCA to improve the science base for risk evaluations and other assessments under the law. This amendment gives EPA authority to issue test orders as well as rules to require manufacturers and processors to generate information on the risks of chemical substances and mixtures.

EPN strongly recommends that EPA add a pre-prioritization process in which test orders are issued to companies to fill critical data gaps for chemicals *before* they advance to prioritization and risk evaluation and get caught up on the deadline-driven production line.

B. Risk Evaluation

The topics covered in this section are based upon our experiences with the review of the scope, problem formulation, and draft risk evaluation documents for the first ten chemicals and scope documents for the second twenty chemicals.

1. Systematic review

Beginning with the review of the first of the initialten draft risk evaluations to be released for comment (PV29) and continuing through release of the other nine risk evaluations, EPN and a host of other commenters repeatedly criticized the use of unvetted,

deeply-flawed systematic review guidance for study identification, selection, and review and for evidence integration. Regrettably, this approach was applied in all ten risk evaluations, with no apparent remedial modifications along the way. Only *after* all ten draft risk evaluations were issued did EPA finally solicit a peer review of the draft guidance — by a committee of the National Academies of Sciences, Engineeringand Medicine. The committee's assessment of the draft guidance can be summed up in the following quote from its February 2021 report[4]: "The OPPT approach to systematic review does not adequately meet the state of the practice. The committee suggests that OPPT comprehensively reevaluate its approach to systematic review methods, addressing the comments and recommendations of Chapter 2."

EPN, of course, was heartened to learn that the agency has already stated its intention NOT to use the 2018 draft guidance going forward. However, concern remains on the matter of what process *will* be used for the next 20 chemicals, Asbestos Part 2, and the three chemicals and one category that are the subject of manufacturers' requests. It is clear that a substantial amount of work is required to bring the guidance to the point where it achieves the state-of-the-practice for systematic review, a status that requires certification of the revised approach via a second external peer review. And, all the while, the clock is ticking on all 25 risk evaluations.

2. Legacy uses and their associated disposal

EPA stated explicitly in the 2017 final Risk Evaluation rule that it would exclude consideration of legacy uses and their associated disposal in all risk evaluations. However, as the agency notes in its OTNE Possible COUs document, "In 2019, the Ninth Circuit Court of Appeals ruled that EPA cannot categorically exclude "legacy use" and "associated disposal" from the definition of "conditions of use.....As a result of the court's opinion, EPA will no longer exclude legacy use or associated disposal from the definition of COUs for chemical risk evaluations."

EPN is aware that a remedy is being attempted, in the current round of evaluations, for asbestos, the best known example in the legacy uses and disposal debate. But it is less clear what steps are being taken or will be taken to identify and incorporate review of legacy uses and their associated disposal for all other chemicals — past, present and future.

We recommend that, beginning immediately with the 25 chemicals for which the review process is still in its early stages, every scope document and risk evaluation include a stand-alone section on legacy uses in which the agency describes what efforts were made to identify them and their associated disposal. All those identified would then be assessed along with the existing uses in the risk evaluation. Those posing an unreasonable risk would be subject to risk management along with any existing COUs for which the same finding

[4] NASEM. 2021 National Academies of Sciences, Engineering, and Medicine. The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. Washington, DC: The National Academies Press. https://doi.org/10.17226/25952.

was made. A similar approach also should be applied to future manufacturer requests and new sets of High Priority chemicals going forward.

3. EPA must account for the lack of adequacy of a toxicitydatabase in the derivation of benchmark margins of exposure.

In conducting risk evaluations in the Existing Chemicals Review program, EPA employs a margin-of-exposure (MOE) approach when characterizing non-cancer risks for human health. The MOE is the ratio of the point of departure(POD) concentration divided by the measured, modelled, or estimated human exposure concentration for each COU assessed in a risk evaluation. Each MOE is then compared to the benchmark MOE which serves as the metric for determining whether or not a COU constitutes an unreasonable risk in each acute and/or chronic exposure scenario. The benchmark MOE is the multiple of a number of uncertainty factors, selected and applied on the basis of the nature of the toxicity database that underlies its calculation. It also should accommodate for the completeness of that database. The benchmark MOE should be identical to the multiplier of uncertainty factors that would be applied to a POD in the derivation of toxicity values such as the oral or dermal reference dose (RfD) or inhalation reference concentration (RfC).

Regrettably, when conducting the risk evaluations for the first ten chemicals, EPA chose to ignore long-standing agency-wide consensus guidance on considering the adequacy of a toxicity database when deriving margins of exposure, RfDs, and RfCs[5,6,7]. As a result, the agency underestimated, often to a significant degree, the magnitude of the risk a COU constituted. There are a number of cases of chemicals(at least four of the ten) where, had an additional uncertainty factor for database deficiency been incorporated into the derivation of the benchmark MOE, the finding for at least one COU scenario would have shifted to "unreasonable risk" from "no unreasonable risk. "

Going forward, EPA has the responsibility to be more transparent and thorough as to what information it needs to assure robust understanding of a chemical's human hazard profile. As noted above, EPA has signaled that it wants information in 13 areas of toxicity in order to support the development of a robust human health hazard assessment in a risk evaluation. To reprise, these are the following: acute toxicity; irritation/corrosion; dermal sensitization; respiratory sensitization; reproductive toxicity; developmental toxicity; genetic toxicity; repeated dose toxicity; carcinogenicity; immunotoxicity; neurotoxicity including developmental; toxicokinetics; and epidemiological and/or biomonitoring studies. The absence of credible empirical data or of validatedcomputational and extrapolation tools

[5] Dourson, ML; Knauf, LA; Swartout, JC. (1992) On reference dose (RfD) and its underlying toxicity database. Toxicol Ind Health 8:171–189.
[6] U.S. EPA. 2002. Review of the Reference Dose and Reference Concentration Processes. Final Report December 2002 EPA/630/P-02/002F Washington, DC.
[7] U.S. EPA. 2002. Review of the Reference Dose and Reference Concentration Processes. Final Report December 2002 EPA/630/P-02/002F Washington, DC.

obligates the agency to account for the deficiency by incorporating a database uncertainty factor >1X (UF_D > 1X) into the calculation of the benchmark margins of exposure.

4. **To produce a truly credible risk assessment, EPA must aggregate exposure within and between COUs and between COUs and the ambient environment in human health risk assessments.**

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). In the real world, people may be exposed to chemical(s) of concern in a work setting and/or as a consumer/ bystander of a product as well as through the ambient environment (air, soil, water). Similarly, ecological receptors may be exposed to chemical(s) of concern as a consequence of environmental releasesrelated to COUs as well as through other sources in the ambient environment. A robust, ethical risk evaluation carried out under TSCA would incorporate both of these source categories into exposure assessments.

For human health impacts, most of the risk evaluations present risk assessments and risk determinations for acute and chronic inhalation and dermal exposures to workers and acute and chronic inhalation exposure to occupational non-users (ONUs), and for acute inhalation and dermal exposures to consumers and sometimes (acute) inhalation and, less often, dermal exposure to bystanders. Generally, oral exposure assessments are not performed for any worker/ONU or consumer/bystander COU, even in circumstances where individuals may engage in hand-to-mouth behaviors. This would likely be more applicable to bystanders who are in younger age groups.

Every one of the first ten risk evaluations contains a section in which the agency states that they must describe whether or not they have considered aggregate exposures in the assessments. However, EPA did not conduct such an assessment or make findings of (no) unreasonable risk based upon combined (aggregate) exposures for most of the first ten chemicals, 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. The agency separately evaluated exposures to the chemical of interest by the inhalation and dermal routes, even though it acknowledged that inhalation and dermal exposures can be assumed to occur simultaneously for both workers and consumers. As the agency stated early on, "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." EPA provided a rationale for not proceeding with aggregate assessments 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 lead" is a more appropriate word than "may lead," in this instance. Aggregation can be done quite easily under these conditions, and the uncertainties can be accommodated. The Office of Pesticide Programs (OPP) has been incorporating multi-route aggregate exposure assessment into their human health risk assessments as standard practice for the past 25

years — because they must. It is mandated in the 1996 Food Quality Protection Act (FQPA).

Furthermore, it is possible that some people may be exposed to the chemical of concern via more than one COU in the same time frame. This second dimension of COUs should also be taken into account, and aggregate exposure assessments should be developed for those scenarios with significant potential for overlap.

But, as pointed out above, COUs may not be the only source of exposure to a chemical of concern. The chemical may very well be present in the ambient environment as the result of past manufacturing, processing, distribution, use, disposal, or other activities. EPA has argued that the agency needn't consider these exposures because they are handled under statutes other than TSCA. It has claimed that it is exercising its TSCA authorities to tailor the scope of its risk evaluations, rather than focusing on environmental exposure pathways addressed under other EPA-administered statutes or regulatory programs or risks that could be eliminated or reduced to a sufficient extent by actions taken under other EPA-administered laws. The reality is that this becomes a false argument, given that the agency has been lax in exercising those responsibilities. In any case, it does not mean that people are not being exposed through the ambient environment at the same time they are being exposed via one or more COU because no regulatory standard is set at zero.

EPN strongly urges the agency to revise its exposure assessment approach when evaluating the risk potential of the COUs associated with a chemical of concern to reflect real world circumstances. Such an approach would address exposure in three dimensions: 1) All routes associated with a single COU; 2) All routes associated with a combination of COUs to which an individual is highly likely to be exposed; and 3) Inclusion of exposures from the ambient environment in the assessment of single (Scenario 1) or multiple (Scenario 2) COUs. Oral exposures should be included, when appropriate, not simply summarily ignored.

5. **EPA should conduct cumulative human health risk assessments under some circumstances.**

EPA defines cumulative risk as "the combined risks from aggregate exposures to multiple agents or stressors."[8]

As EPN argued in its comments on the Scope 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) Closestructural similarities, e.g., members of the same chemical class; 3) Shared metabolic pathways and byproducts of metabolism; 4)

[8] U.S. EPA. 2003. Framework for Cumulative Risk Assessment. U.S. Environmental Protection Agency, Office of Research and Development, Center for Public Health and Environmental Assessment (CPHEA), formerly known as the National Center for Environmental Assessment (NCEA), Washington Office, Washington, DC, EPA/600/P-02/001F. Available at https://www.epa.gov/risk/framework-cumulative-risk-assessment

Similar toxicity profiles; and 5) Similar modes/mechanisms of action of shared toxicity endpoints.

EPA's failure to consider aggregate exposure and cumulative exposure 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 date, to consider concomitant exposures in media/scenarios covered by regulatory measures under other statutes, such as air emissions, drinking water and waste-related exposures.

There are a number of specific scenarios for which the agency should now be conducting cumulative risk assessments in the Existing Chemicals Review Program. Others will present themselves as additional chemicals are added to subsequent High Priority listings.

Scenario 1 is the combined assessment of certain chlorinated volatile organic compounds (VOCs). The trichloroethylene (TCE) risk evaluation includes a detailed discussion of the (mammalian) toxicokinetics (absorption, distribution, metabolism, and excretion) of that substance. It notes that it shares metabolites in common with a number of other chlorinated VOCs, most of which are currently subject to the TSCA risk evaluation process. Those listed in Table 3-4 of the TCE final risk evaluation (p. 230) include perchloroethylene; 1,1,2,2- tetrachloroethane; trichloroethylene; 1,1,1-trichloroethane; 1,2-dichloroethylene; and 1,2-dichloroethane. These chemicals also exhibit similarities in their hazard profiles with some of their adverse outcomes likely caused by common modes of action.

The chemicals listed in Table 3-4 meet most, perhaps all, of the criteria. Therefore, the agency should consider conducting cumulative assessments when their COUs, exposed (sub)populations, metabolites, adverse effects, and modes of action overlap.

Scenario 2 is the combined assessment of eight phthalates: five on the list of the Next 20; Di-n-octyl phthalate (DnOP), which is on the 2014 Work Plan but left off the Next 20 list; and Diisodecyl phthalate (DIDP) and Diisononyl phthalate (DINP), for which manufacturer's requests have been submitted and granted.

The eight phthalates have in common a number of toxicity endpoints of concern, each of which could be the focus of cumulative assessments. There is precedent for exercising this approach as seen in the 2008 National Academies of Science report *Phthalates and Cumulative Risk Assessment: The Task Ahead* and in the Consumer Product Safety Commission's July 2014 report of the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives. Some minimal effort has been extended outside of the OPPT to apply some of the lessons from the NAS report, but no agency-wide consensus exists on a unified approach (see, for example, Christensen KL, Makris SL, Lorber M. Generation of hazard indices for cumulative exposure to phthalates for use in cumulative risk assessment. Regul Toxicol Pharmacol. 2014 Aug;69(3):380-9. doi: 10.1016/j.yrtph.2014.04.019. Epub 2014 May 9). OPPT's sister office in OCSPP (OPP) has substantial experience with conducting cumulative risk assessments under the FQPA legislative mandates.

EPA (OPPT) has, in fact, articulated its own concern about these eight phthalates in its 2012 Phthalates Action Plan: "EPA is concerned about phthalates because of their toxicity and the evidence of pervasive human and environmental exposure to them. Thus, EPA intends to initiate action to address the manufacturing, processing, distribution in commerce, and/or use of these eight phthalates. EPA intends to take action as part of a coordinated approach with the Consumer Product Safety Commission (CPSC) and the Food and Drug Administration (FDA)."

6. **EPA should consider conducting aggregate and cumulative assessments for ecological targets under some circumstances.**

Ecological impacts generally occur as a consequence of a single COU — disposal (that is, environmental release), which invariably is included as a COU for chemicals undergoing risk evaluation. EPA generally conducts acute and chronic assessments and provides risk estimations for aquatic species but not always quantitative assessments for sediment organisms. Also, it less often analyzes releases to land, including biosolids application to soil or exposure of terrestrial organisms through soil, land-applied biosolids, or ambient air.

Ecological targets may be exposed to a single chemical in the aggregate and also could be exposed to multiple chemicals in the cumulative. We believe that EPA should also conduct ecological aggregate assessments to a single chemical and cumulative assessments of similar chemicals, using the same criteria as developed for human health. EPA should begin this by exploring cumulative assessments for Chemical Group Scenarios 1 and 2.

7. **EPA should make its determinations of (No) Unreasonable Risk for workers based upon the assumption that personal protective equipment (PPE) is not being used.**

EPN (and many others) find problematic the agency policy that when it projects unreasonable risk for workers, it often dismisses that risk finding 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, effective, or used.

This last point was demonstrated in the example of HBCD, which has no OSHA permissible exposure limit or National Institution of Occupational Safety and Health standard. EPA still overrode the risks to workers by assuming constant use of respirators and gloves. The more prudent public health approach would be to make all "Unreasonable Risk" findings based upon the expectation that the workers are not using PPE.

8. **Coordination of peer review with the public comment period.**

The final Risk Evaluation Rule (82 FR 33726 (July 20, 2017)) makes quite clear the agency's official position on the appropriate relationship between the scheduling of the public comment period for a risk evaluation and the timing of meetings of the Science Advisory Committee on Chemicals (SACC), the TSCA-mandated external expert science peer review body: "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."

On *NO* occasion during the development of the risk evaluations for any of the first ten chemicals was the agency in compliance with its own policies on public comment and peer review. In every case, the peer review meeting (in person for the first seven chemicals, virtually for the remaining three in light of the COVID-19 pandemic) was held while the public comment period was still open, a situation clearly inconsistent with best management practices and the agency's own peer review principles, as articulated in its Peer Review Handbook.[9] It was always a rush for a public commenter to assemble and submit at least some preliminary thoughts on the chemical being scrutinized before a SACC meeting.

This process as implemented deprived the SACC of scientific and policy input that would have been valuable in informing its review of the draft risk evaluations and, thus, it greatly reduced the value of the public comment process. This recurrence reinforced the view that the agency approach, at the time, valued a calendar deadline over the integrity of the information going into a product or decision and represented yet another example of disdain for the scientific enterprise. Furthermore, the process appeared to be a mechanism to discourage comments from the stakeholder community.

EPN strongly recommends that, going forward, beginning with the risk evaluations for the 25 chemicals/category currently or soon to be underway, the agency readjust the timing of the public comment period and the peer review so that the latter does not occur until the public comment period has closed and all comments have been made available to the peer reviewers for their consideration. It is critical that the agency assure the integrity of the Existing Chemical Review program; taking this step is one measure toward achieving that goal.

C. Risk Management

1. EPA should proceed with a total ban on asbestos.

It has been clear for many decades that asbestos poses a very serious risk to human health. It is a potent human carcinogen.

Mixed results have occurred when EPA has attempted to mitigate risk to asbestos under TSCA. EPA promulgated the Asbestos Ban and Phase Out Rule in 1989. This rule was largely vacated shortly thereafter. The most recent action came in April 2019 when EPA finalized an Asbestos Significant New Use Rule (SNUR) under TSCA Section 5, which prohibits manufacturing (including importing) or processing of discontinued uses of asbestos from restarting without EPA having an opportunity to evaluate each intended use for risks to health and the environment, and to take any necessary regulatory action, which

[9] U.S. EPA. 2015. U.S. Environmental Protection Agency. Peer Review Handbook. 4th Edition. Science and Technology Policy Council. EPA/100/B-15/001.Washingotn, DC. Available at: https://www.epa.gov/sites/production/files/2020-08/documents/epa_peer_review_handbook_4th_edition.pdf

may include a prohibition. Given that this does not represent a permanent ban, the possibility exists that importing, processing, or manufacturing as well as discontinued uses could be approved in the future.

The December 2020 Chrysotile Asbestos risk evaluation concludes that most of the conditions of use evaluated pose an unreasonable risk to public health: all consumer (users and bystanders) and most occupational (workers and ONUs) settings.

It is time to proceed directly to rulemaking with a proposal to ban the importation, manufacture, processing, distribution, and use of all forms of asbestos for all commercial and consumer uses in the U.S. on an expedited timeline. Over 30 years have passed since the 1989 rule failed, during which alternatives could have been developed. There is no reason for delaying action any further.

2. **EPA should reinstitute rulemaking on the three chemicals relegated to limbo during the Trump administration.**

Few substantive measures have been taken to mitigate unreasonable risks associated with exposure to chemicals that are being assessed in the Existing Chemicals Review Program mandated in the amendedTSCA. Prior to the transition to the Trump administration, as late as mid-January 2017, the agency had issued proposals for three chemicals later selected as High Priority chemicals in the first round of review (trichloroethylene, methylene chloride, and N-methylpyrrolidone). Those proposed rules gathered dust for four years, only to be wiped off the agency's regulatory agenda in late December 2020, forcing EPA to start the rulemaking process all over again.

The unreasonable risks identified before 2017 remain. Others have likely been identified during the process of developing their respective risk evaluations. All those identified should be incorporated into renewed rulemaking.

3. **Going forward, EPA should take immediate steps to address serious acute risks identified during the development of risk evaluations.**

No risk mitigation measures were pursued in those instances in which the agency identified significant acute risks during the development of the first ten risk evaluations. EPA brushed off requests from EPN (and others) immediately to address acute risks associated with 1-bromopropane and methylene chloride and not to wait for the completion of a multiyear risk management rulemaking. In letters to Administrator Wheeler, EPN urged the agency to use its statutory authority to propose and promulgate rules under Section 6(a) and to expedite their effective dates under Section 6(d).

4. **EPA-sponsored Risk Management webinars, as presented, were of minimal value and should be modified or abandoned.**

Following the issuance of final risk evaluations for some of the first ten chemicals, EPA sponsored virtual meetings during which they summarized the findings in the risk

evaluation, but little else. These events proved to be of questionable value, as the findings are summarized in each final risk evaluation and, more succinctly, in each Non-technical Summary document.