October 25, 2021

Comments on Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act

Submitted online via Regulations.gov to docket EPA-HQ-OPPT-2018-0443

The following comments are being submitted by the undersigned scientists, academics, and clinicians. We have no direct or indirect financial or fiduciary interest in the manufacture or sale of any chemical or product that is the subject of these comments.

We appreciate the opportunity to provide written comments on the scoping document for EPA's manufacturer-requested risk evaluation on octamethylcyclotetrasiloxane (D4), pursuant to the Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act. [1]

D4 is a commercial chemical used in the production of silicones and rubbers commonly found in cosmetics, hair care products and deodorants.[2,3] While the data on the health impacts of D4 are limited, regulatory agencies in the United Kingdom, [4] Canada, [5] and the European Union[6] have all have classified it as persistent, bioaccumulative, and toxic and found that D4 is dangerous for the environment and may cause long-term adverse effects to fish and invertebrates in the aquatic environment. In research relevant to human health, D4 is associated with adverse reproductive health outcomes such as a risk of impaired fertility. Specifically, D4 mimics the female hormone estrogen in laboratory animals following oral exposure to low doses of D4.[7]

In March 2020, the European Chemicals Agency (ECHA) prohibited the sale of products containing D4, D5, and D6 at concentrations greater than 0.1%.[8] The prohibition covers both leave-on personal care products and other consumer or professional products as well as wash-off personal care products.[9]

In August 2020, we commented on the draft risk evaluation for D4 prepared by Silicones Environmental, Health, and Safety Center (SEHSC) as a part of the manufacturer-requested risk evaluation and noted the evaluation contained multiple methodological and scientific flaws.[10] Although TSCA mandates that

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[1] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments). Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

[2] National Center for Biotechnology Information (2020). PubChem Compound Summary for CID 11169, Octamethylcyclotetrasiloxane. Retrieved July 29, 2020 from https://pubchem.ncbi.nlm.nih.gov/compound/Octamethylcyclotetrasiloxane.

[3] See http://www.silicones-europe.com/ab_facts.html

[4] Brooke DN, Crookes MJ, Gray D, Robertson S (2009) Environmental risk assessment report: octamethylcyclotetrasiloxane. UK Environment Agency, Bristol

[5] Environment Canada, Health Canada (2008) Screening assessment for the challenge: octamethylcyclotetrasiloxane (D4). CAS RN 556-67-2, Environment Canada

[6] ECHA's committees conclude on five restrictions - All news. (n.d.). Retrieved July 29, 2020, from https://echa.europa.eu/-/echa-s-committees-conclude-on-five-restrictions.

[7] National Center for Biotechnology Information (2020). PubChem Compound Summary for CID 11169, Octamethylcyclotetrasiloxane. Retrieved July 29, 2020 from https://pubchem.ncbi.nlm.nih.gov/compound/Octamethylcyclotetrasiloxane.

[8] ECHA's committees conclude on five restrictions - All news. (n.d.). Retrieved July 29, 2020, from https://echa.europa.eu/-/echa-s-committees-conclude-on-five-restrictions.

[9] Hogue, C. (2019, January 17). EU proposes to restrict some siloxanes, formaldehyde, and microplastics. Retrieved July 29, 2020, from https://cen.acs.org/policy/regulation/EU-proposes-restrict-siloxanes-formaldehyde/97/i3

[10] US EPA. (2020). Manufacturer Request for Risk Evaluation under the Toxic Substances Control Act: Octamethylcyclotetra-siloxane (D4). Comment submitted by Swati Rayasam et al, Science Associate, Program on Reproductive Health and the Environment, Department of

EPA use the "best available science,"[11] we had concerns about EPA's ability to apply the same standards to the manufacturer-requested risk evaluation if it used the SEHSC draft risk evaluation to inform its risk evaluation process regarding D4.[12] We also urged EPA to include all intended, known or reasonably foreseen conditions of use and to utilize its authorities for testing and data gathering under TSCA sections 4 and 8.

There are important improvements in the Agency's approach to conducting a risk evaluation in this current scope compared to past practice. EPA plans to include all conditions of use and all exposure pathways in the risk evaluation, without claiming discretion to exclude uses or exposures. EPA also stated that it is not assuming the use of Personal Protective Equipment (PPE) when making unreasonable risk determinations but plans to include analysis on the impact of PPE on exposures for the purpose of informing potential risk management decisions. Finally, the draft scope acknowledges the need for EPA to conduct further work to identify potentially exposed or susceptible subpopulations (PESS) in order to meet its mandate under TSCA and is clear that this work is critical to addressing the EPA priority of environmental justice.[13,14] These improvements represent significant and health-protective changes that we support. However, as discussed in the detailed comments below, there is still further work to be done in defining the scope to ensure a complete risk evaluation that does not underestimate risks of D4.

Our comments address the following main issues:

1. **EPA must address potentially exposed or susceptible subpopulations more robustly to adequately consider exposure risks.**
2. **EPA must consider every exposure scenario and fully aggregate all possible sources, pathways, and routes of exposures (including non-TSCA uses), to accurately estimate human health risks of D4, including for potentially exposed or susceptible subpopulations.**
3. **The studies that EPA is using to understand D4's persistence in the environment are not accurately approximating real-world values and thus do not represent the "best available science."**
4. **The D4 risk evaluation must assess risks from human and environmental exposure to D4 degradation products, and the scope document must be revised accordingly.**
5. **The draft Analysis Plan for D4 is lacking in important details, including clear statements of the intended outputs for each major element of the planned risk evaluation.**
6. **The approaches to dose-response assessment and risk characterization in the analysis plan needs to be clarified and expanded.**

We appreciate the opportunity to provide public input. Please do not hesitate to contact us with any questions regarding these comments.

Sincerely,

Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco (UCSF). Available: https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0443-0013

[11] 15 USC §2625(h)

[12] 15 USC §2605(b)(4)(C) and 15 USC §2605(b)(4)(E)(ii) "…the Administrator shall not expedite or otherwise provide special treatment to such risk evaluations."

[13] Freedhoff, Michal. (2021). "The Promise of TSCA" Available: https://mcusercontent.com/638d8b68a755a4e4bab7143ad/files/79047715-a4e8-457b-8561-fa1432c082c6/MICHAL_TSCA_SPEECH.pdf

[14] US Executive Office of the President: Executive Order on Tackling the Climate Crisis at Home and Abroad § 219. In.; 2021.

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DETAILED COMMENTS:

1. **EPA must address potentially exposed or susceptible subpopulations more robustly to adequately consider exposure risks.**

Scientific evidence demonstrates that intrinsic and extrinsic factors can change exposures and susceptibility to environmental chemical exposure risks.[15,16] Intrinsic factors, such as physiological parameters specific to life stage, may make individuals more or less vulnerable to environmental exposures.[17,18] For example, young infants (less than three months old) have lower lipid content with respect to adults (reducing their relative retention of lipophilic chemicals) while older infants have higher lipid content with respect to adults (increasing their relative retention of lipophilic chemicals). Extrinsic factors, including social stressors, lack of access to health care facilities,[19,20,21] healthy food,[22,23] health information, and adequate formal education opportunities for health literacy[24] can compound the negative effects of environmental exposures among these subpopulations.

Amended TSCA mandates that EPA consider the impacts of chemical exposures on potentially exposed or susceptible subpopulations (PESS). PESS is defined in TSCA section 3(12) as:

> *"…a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population for adverse health effects from exposure to a chemical substance or mixture, such as children, women who are or may become pregnant, workers, or the elderly."*

EPA has previously acknowledged the importance of accurately identifying PESS, noting that incorrectly identifying PESS impacted at least six of the first 10 chemical risk evaluations and recently (June 2021) announcing plans to re-examine to what extent the previous decisions to exclude exposure from air or water pathways from risk evaluations fail to identify and protect fenceline communities.[25] We commend EPA for recognizing that PESS identification requires further work.

EPA identifies the following groups as PESS for D4: *"children, women of reproductive age (e.g., women who are or may become pregnant), workers, ONUs, consumers and bystanders, and indigenous, native*

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[15] Shaffer, R. M.; Smith, M. N.; Faustman, E. M., Developing the Regulatory Utility of the Exposome: Mapping Exposures for Risk Assessment through Lifestage Exposome Snapshots (LEnS). Environmental Health Perspectives 2017,125, (8), 085003. https://doi.org/10.1289/EHP1250v

[16] Institute of Medicine (US) Committee on Quality of Health Care in America. To Err is Human: Building a Safer Health System. Kohn LT, Corrigan JM, Donaldson MS, editors. Washington (DC): National Academies Press (US); 2000. https://doi.org/10.17226/9728

[17] Axelrad DA, Setzer RW, Bateson TF, DeVito M, Dzubow RC, Fitzpatrick JW, et al. Methods for evaluating variability in human health dose–response characterization. Human and Ecological Risk Assessment: An International Journal. 2019;0:1–24. https://doi.org/10.1080/10807039.2019.1615828

[18] Hines RN, Sargent D, Autrup H, Birnbaum LS, Brent RL, Doerrer NG, et al. Approaches for assessing risks to sensitive populations: lessons learned from evaluating risks in the pediatric population. Toxicol Sci. 2010;113:4–26. https://doi.org/10.1093/toxsci/kfp217

[19] 2018 National Healthcare Quality and Disparities Report. Agency for Health Research and Quality [Internet]. [cited 2020 Aug 8]. Available from: https://www.ahrq.gov/research/findings/nhqrdr/nhqdr18/index.html

[20] Institute of Medicine. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care [Internet]. 2002 [cited 2020 Aug 2]. Available from: https://www.nap.edu/catalog/12875/unequal-treatment-confronting-racial-and-ethnic-disparities-in-health-care

[21] Shi L, Chen C-C, Nie X, Zhu J,Hu R. Racial and Socioeconomic Disparities in Access to Primary Care Among People with Chronic Conditions. J Am Board Fam Med. American Board of Family Medicine; 2014;27:189–98. https://doi.org/10.3122/jabfm.2014.02.130246

[22] Hilmers A, Hilmers DC, Dave J. Neighborhood Disparities in Access to Healthy Foods and Their Effects on Environmental Justice. Am J Public Health. 2012;102:1644–54. https://doi.org/10.2105/AJPH.2012.300865

[23] Walker RE, Keane CR, Burke JG. Disparities and access to healthy food in the United States: A review of food deserts literature. Health & Place. 2010;16:876–84. https://doi.org/ 10.1016/j.healthplace.2010.04.013

[24] National Academies of Sciences, Engineering, and Medicine. Monitoring Educational Equity [Internet]. 2019 [cited 2020 Aug 2]. Available from: https://www.nap.edu/catalog/25389/monitoring-educational-equity

[25] US Environmental Protection Agency, EPA Announces Path Forward for TSCA Chemical Risk Evaluations In 2021.

populations."[26] We agree with the inclusion of these groups, however this list fails to account for individuals with chronic conditions and people who live or work near manufacturing, processing, use, or disposal sites. Further, given that D4 is used in personal care products, we recommend that EPA consider differences in use by race/ethnicity given that previous research finds that certain populations can have higher exposures via personal care products.[27] These individuals must also be considered PESS.

To facilitate improved methods for identifying PESS, EPA must follow through on its outlined plans in the D4 scope to evaluate reasonably available evidence on:

> *"factors that may make population groups of concern more vulnerable to adverse effects (e.g., unique pathways; cumulative exposure from multiple stressors; and behavioral, biological, or environmental factors that increase susceptibility)"* and *"to determine whether some human receptor groups may be exposed via exposure pathways that may be distinct to a particular subpopulation or life stage (e.g., reproductive age females who may be or become pregnant, lactating women, infants, toddlers, children at various developmental stages in life, and elderly) and whether some human receptor groups may have higher exposure via identified pathways of exposure due to unique characteristics (e.g., activities, duration or location of exposure)…"*[28]

EPA must account for these combined exposures and risks from multiple roles related to the conditions of use (e.g., a woman of reproductive age who works in the production of D4, who uses consumer products containing D4, and lives near a manufacturing, processing, distribution, use, or disposal site for D4). Analyzing the impact of compounding factors is critical to understanding the health risks of exposure when considering D4, which is discussed further in point #2 (below) on aggregate exposures. EPA should also account for exposure to multiple related stressors (e.g., considering chemical classes and mixtures rather than a chemical-by-chemical approach and evaluating cumulative exposure to non-chemical stressors). The 2004 National Environmental Justice Advisory Council (NEJAC) report on cumulative risk assessment emphasized that incorporating the full range of stressors to which populations are exposed is key to understanding community risk and community health.[29] This is consistent with recommendations from the National Academy of Sciences (NAS)[30,31,32] and the published literature[33] which report that default approaches to treatment of human variability in risk assessments need to be updated to better incorporate current knowledge regarding human variability and vulnerability factors.

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[26] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 40. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

[27] Zota AR, Shamasunder B. The environmental injustice of beauty: framing chemical exposures from beauty products as a health disparities concern. Am J Obstet Gynecol. 2017 Oct;217(4):418.e1-418.e6. doi: 10.1016/j.ajog.2017.07.020. Epub 2017 Aug 16. PMID: 28822238; PMCID: PMC5614862

[28] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 40. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

[29] National Environmental Justice Advisory Council Cumulative Risks/Impacts Work Group. (2004). Ensuring Risk Reduction in Communities with Multiple Stressors: Environmental Justice and Cumulative Risks/Impacts [Internet]. Available from: https://www.epa.gov/sites/default/files/2015-02/documents/nejac-cum-risk-rpt-122104.pdf

[30] National Research Council. Toxicity Testing in the 21st Century: A Vision and a Strategy [Internet]. Washington, D.C.: The National Academies Press; 2007. Available from: https://www.nap.edu/download/11970#

[31] National Research Council. Phthalates and Cumulative Risk Assessment: The Task Ahead [Internet]. Washington, D.C.: The National Academies Press; 2008 [cited 2011 Oct 15]. Available from: https://doi.org/10.17226/12528

[32] National Research Council. Science and Decisions: Advancing Risk Assessment [Internet]. Washington, D.C.: The National Academies Press; 2009 [cited 2011 Oct 15]. Available from: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=202175

[33] Chiu WA, Rusyn I. Advancing chemical risk assessment decision-making with population variability data: challenges and opportunities. Mamm Genome. 2018;29:182–9. https://doi.org/10.1007/s00335-017-9731-6

We also continue to recommend the EPA explicitly adopt an expanded definition of PESS that highlights the role of intrinsic and extrinsic factors that influence susceptibility. This would complement EPA's plans to *"increase consideration of environmental justice issues."*[34] Our recommended definition, a modification of the definition found in the January 2017 proposed TSCA risk evaluation framework rule,[35] is as follows:

> *"Potentially susceptible subpopulation means a group of individuals or communities within the general population who, due to greater susceptibility, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, including but not limited to infants, children, pregnant women, workers, or the elderly. Susceptibility can be due to both intrinsic (e.g., life stage, reproductive status, age, gender, genetic traits) and acquired (e.g., pre-existing disease, geography, socioeconomic, racism/discrimination, cultural, workplace) factors when identifying this population."*

We look forward to reviewing documents outlining how EPA plans to address PESS more robustly and encourage the agency to incorporate guidance from the Children's Health Protection Advisory Committee (CHPAC), the White House Environmental Justice Advisory Council (WHEJAC), the NEJAC, and directly impacted environmental justice communities.

2. EPA must consider every exposure scenario and fully aggregate all possible sources, pathways and routes of exposures (including non-TSCA uses), to accurately estimate human health risks of D4, including for potentially exposed or susceptible subpopulations

When conducting a risk evaluation, Amended TSCA requires EPA to:

> *"integrate and assess available information on hazards and exposures **for the conditions of use of the chemical substance**, including information that is relevant to specific risks of injury to health or the environment and information on potentially exposed or susceptible subpopulations and describe whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered, and the basis for that consideration"*[36]

and eliminate the unreasonable risk posed by a chemical substance from:

> *"the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance or mixture, **or any combination of such activities**."*[37]

EPA describes numerous categories of conditions of use in its draft scope of D4 (*Table 2-2. Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation*), including manufacturing, processing, and consumer uses.

Not included in this list of conditions of use, are certain non-TSCA uses of D4, which EPA is potentially considering not evaluating under the current D4 scope risk assessment, which includes:

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[34] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 40. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

[35] Federal Register 7562 (January 19, 2017) [FRL-9957-75] https://www.federalregister.gov/documents/2017/01/19/2017-01224/procedures-for-chemical-risk-evaluation-under-the-amended-toxic-substances-control-act

[36] US Environmental Protection Agency, Toxic Substances Control Act (TSCA). In Vol. 15 USC ch. 53 subch. I §§ 2601–2629.

[37] US Environmental Protection Agency, Toxic Substances Control Act (TSCA). In Vol. 15 USC ch. 53 subch. I §§ 2601–2629.

- *"Food packaging materials which meet the definition for a "food additive" described in section 201 of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 321".*
- *"Dental bonding agents and breast implants which meets the definition of "device" under section 201 of the FFDCA, 21 U.S.C. 321".*
- *"Personal care products that meet the definition of "cosmetics" under section 201 of the FFDCA, 21 U.S.C. 321.".*
- *"D4 used in over-the-counter medication which meets the definition of a "drug" in section 201 of the FFDCA, 21 U.S.C. 321"*

EPA also states that:

> "*As described in the preamble to the Risk Evaluation Rule (See Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act, 33726 Fed. Reg. 33735 (July 20, 2017), EPA may consider potential risk from non-TSCA uses in evaluating whether a chemical substance presents an unreasonable risk. Although EPA would not regulate non-TSCA uses, the potential exposures of non- TSCA uses may help inform the Agency's risk determination for the exposures from uses that are covered under TSCA (e.g., as background exposures that would be accounted for, should EPA decide to evaluate aggregate exposures).*"

This preamble to the Risk Evaluation Rule is important because the EPA's analysis plans states that it will:

> "***Map or group each condition of use to a release assessment scenario(s).*** *EPA has completed initial mapping of release scenarios to relevant conditions of use as shown in Appendix F. EPA plans to refine the mapping/grouping of release scenarios based on factors (e.g., process equipment and handling, magnitude of production volume used, and exposure/release sources) corresponding to conditions of use using reasonably available information. EPA may perform supplemental targeted searches of peer-reviewed or gray literature to better understand certain conditions of use to further develop these release scenarios.*"

Comprehensive evaluation of release scenarios is important, and it should be accompanied by aggregation of all potential sources of exposures across each condition of use, including non-TSCA uses of D4 in order to fully assess potential health risks.

When evaluating the level of exposure an individual may experience from D4, EPA should not focus on only a single pathway with the greatest contribution to human exposure to D4**,** but must aggregate these exposures across all pathways and routes of human exposure (e.g., dermal, oral, and inhalation). If EPA ignores any exposure scenarios or does not fully combine all possible sources, pathways, and routes of exposures (including the non-TSCA uses described above), then it will underestimate human health risks of D4, including for potentially exposed or susceptible subpopulations.

When considering all routes of exposure scenarios for conditions of use, EPA should also incorporate aggregate exposure scenarios where some individuals may be exposed to D4 through combinations of occupational, consumer, and general population settings. Similar to aggregating exposure sources across all potential conditions of use, EPA should consider cumulative risk assessment, particularly with D4 secondary degradation products, such as DMSD that may pose human health risks (point # 4 below). Without fully accounting for cumulative risk assessment with metabolites and potential mixtures, EPA will underestimate the health risks of D4.

3. The studies that EPA is using to understand D4's persistence in the environment are not accurately approximating real-world values and thus do not represent the "best available science."

D4 belongs to a group of organosilicon chemicals that are used in a variety of industrial applications and consumer products, called volatile methylsiloxanes (VMS). Their primary use is in personal care products, mainly deodorants, where they are used as carriers for active ingredients. When personal care products are applied on the skin, the largest fraction of VMS volatilizes and degrades by reacting with hydroxyl radicals in the air. However, a smaller but significant fraction is washed down the drain and enters the wastewater system, from where VMS are released into the aquatic environment. VMS have become a point of concern among environmental scientists and regulators due to their continuous presence and long residence times in aquatic environments.

Because of their hydrophobicity, the environmental fate of VMS is controlled by their affinity for organic carbons found in suspended particles in the water column and in sediments. That affinity is described by the organic carbon/water partition ratio (K_{OC}), which is the concentration of a given chemical in organic carbon divided by the concentration of the chemical in water in a closed system at thermodynamic equilibrium. Reported measurements of the K_{OC} of D4 in the literature vary by over half a log unit, which has important implications for calculations of environmental fate and persistence. Depending on which set of values one uses, the modeled residence time of D4 may differ by over 100 days and may or may not exceed regulatory thresholds for persistence. This makes the choice of physicochemical properties critical for the risk assessment of D4 as one can draw different conclusions depending on which set of properties are used.

At the moment, there are two sets of physicochemical properties for D4, i) one set from the studies of Kozerski et al.[38] (Dow Corning) and Xu and Kropscott[39] (Dow Corning), and ii) one set from the studies of Panagopoulos Abrahamsson et al. (Stockholm University) Previous studies by Krogseth et al.[40] and Panagopoulos Abrahamsson et al.[41,42] have shown that when modeling the environmental fate of VMS in aquatic environments, the physicochemical properties of Panagopoulos Abrahamsson et al.[43,44] predict more accurately experimentally measured concentrations of D4 in sediments, while concentration

[38] G. E. Kozerski, S. Xu, J. Miller and J. Durham, Determination of soil-water sorption coefficients of volatile methylsiloxanes, Environ. Toxicol. Chem., 2014, 33(9), 1937.

[39] S. H. Xu and B. Kropscott, Evaluation of the Three-Phase Equilibrium Method for Measuring Temperature Dependence of Internally Consistent Partition Coefficients (K-Ow, K-Oa, and K-Aw) for Volatile Methylsiloxanes and Trimethylsilanol, Environ. Toxicol. Chem., 2014, 33(12), 2702–2710.

[40] I. S. Krogseth, E. Undeman, A. Evenset, G. N. Christensen, M. J. Whelan, K. Breivik and N. A. Warner, Elucidating the Behavior of Cyclic Volatile Methylsiloxanes in a Subarctic Freshwater Food Web: A Modeled and Measured Approach, Environ. Sci. Technol., 2017, 51(21), 12489–12497.

[41] D. Panagopoulos Abrahamsson, N. Warner, L. Jantunen, A. Jahnke, F. Wong, M. MacLeod. Investigating the presence and persistence of volatile methylsiloxanes in Arctic sediments. Environ. Sci.: Processes Impacts, 2020, 22, 908–917.

[42] D. Panagopoulos Abrahamsson and M. MacLeod, A critical assessment of the environmental fate of linear and cyclic volatile methylsiloxanes using multimedia fugacity models, Environ. Sci.: Processes Impacts, 2018, 20(1), 183–194.

[43] D. Panagopoulos Abrahamsson, A. Jahnke, A. Kierkegaard and M. MacLeod, Organic Carbon/Water and Dissolved Organic Carbon/Water Partitioning of Cyclic Volatile Methylsiloxanes: Measurements and Polyparameter Linear Free Energy Relationships, Environ. Sci. Technol., 2015, 49(20), 12161–12168.

[44] D. Panagopoulos Abrahamsson, A. Jahnke, A. Kierkegaard and M. MacLeod, Temperature Dependence of the Organic Carbon/Water Partition Ratios (Koc) of Volatile Methylsiloxanes, Environ. Sci. Technol. Lett., 2017, 4(6), 240–245.

predictions using the properties Kozerski et al.[45] and Xu and Kropscott[46] underestimate concentrations in sediments by more than 2 log units. These findings suggest that calculations of persistence in aquatic environments are expected to be closer to real-world values when using the physicochemical properties of Panagopoulos Abrahamsson et al.[47,48] This is an important finding that needs to be considered in calculations of persistence by the US EPA when assessing the environmental risk posed by D4 and that the default should be to use the study that would best protect the environment.

4. **The D4 risk evaluation must assess risks from human and environmental exposure to D4 degradation products, and the scope document must be revised accordingly.**

According to the draft scope, "*D4 degrades into DMSD [dimethylsilanediol] in water, soil, and sediment via different intermediate degradants under specific field and laboratory conditions*"[49] and "*DMSD has been detected in environmental samples*."[50] Although EPA requests information from the public regarding environmental fate, environmental concentrations, and toxicity of DMSD and other degradation products, the analysis plan does not state how any information regarding DMSD will be used in the risk evaluation. Any risks from exposure to DMSD and other breakdown products must be accounted for in assessing the risks of D4.

A review by Ramanathan et al. found that "Hematotoxicity, hepatotoxicity, and possibly neurotoxicity were the most sensitive toxicological endpoints for DMSD."[51]

5. **The draft Analysis Plan for D4 is lacking in important details, including clear statements of the intended outputs for each major element of the planned risk evaluation.**

An analysis plan is a useful and important tool for outlining the approaches and outputs expected to be addressed in a forthcoming risk evaluation. EPA's 2014 Framework for Human Health Risk Assessment to Inform Decision Making (HHRA Framework)[52] provides guidance for the contents of an analysis plan, including:

- The "Key questions and considerations" for an analysis plan are: "What approaches, methods and metrics will be used to assess exposures, effects and risk, including the associated uncertainty and variability?"

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[45] G. E. Kozerski, S. Xu, J. Miller and J. Durham, Determination of soil-water sorption coefficients of volatile methylsiloxanes, Environ. Toxicol. Chem., 2014, 33(9), 1937.

[46] S. H. Xu and B. Kropscott, Evaluation of the Three-Phase Equilibrium Method for Measuring Temperature Dependence of Internally Consistent Partition Coefficients (K-Ow, K-Oa, and K-Aw) for Volatile Methylsiloxanes and Trimethylsilanol, Environ. Toxicol. Chem., 2014, 33(12), 2702–2710.

[47] D. Panagopoulos Abrahamsson, A. Jahnke, A. Kierkegaard and M. MacLeod, Organic Carbon/Water and Dissolved Organic Carbon/Water Partitioning of Cyclic Volatile Methylsiloxanes: Measurements and Polyparameter Linear Free Energy Relationships, Environ. Sci. Technol., 2015, 49(20), 12161–12168.

[48] D. Panagopoulos Abrahamsson, A. Jahnke, A. Kierkegaard and M. MacLeod, Temperature Dependence of the Organic Carbon/Water Partition Ratios (Koc) of Volatile Methylsiloxanes, Environ. Sci. Technol. Lett., 2017, 4(6), 240–245.

[49] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 36. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

[50] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 35. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

[51] Ramanathan R, James JT, McCoy T. Acceptable levels for ingestion of dimethylsilanediol in water on the International Space Station. Aviat Space Environ Med. 2012 Jun;83(6):598-603. doi: 10.3357/asem.3198.2012.

[52] U.S. EPA 2014. Framework for Human Health Risk Assessment to Inform Decision Making. EPA/100/R-14/001. https://www.epa.gov/risk/framework-human-health-risk-assessment-inform-decision-making

- "The analysis plan is most useful when it contains explicit statements of how measures were selected, what the measures were intended to evaluate and which analyses they support."
- "The analysis plan describes the exposure assessment elements specified in the conceptual model, including the relevant routes and pathways, frequency and duration of exposures, populations and life stages, and assessment metrics."
- "Key limitations, assumptions and uncertainties associated with the tools and approaches are recognized in the analysis plan."
- "The analysis plan also identifies the approach for describing exposure variability."
- "The analysis plan identifies and describes the strategy or approach for combining exposure information with hazard and dose-response information to generate risk estimates or other measures for characterizing health risk."

A comparison of the draft D4 analysis plan with the EPA HHRA Framework document reveals multiple shortcomings. Many elements of the draft analysis plan are extremely vague. EPA now has enough experience with conducting TSCA risk evaluations so that it should easily be able to provide much more detail in the analysis plan regarding approaches and outputs that can be expected in the risk evaluation. This would make the scope document much more useful for EPA and much more informative to the public. It would also provide EPA the opportunity to make any necessary revisions to its approach based on public comment *before* it completes a draft risk evaluation that will then be peer reviewed and subject to public comment.

As an illustration of the shortcomings of the draft analysis plan, the plan for Occupational Exposures (section 2.7.2) provides very limited information; for example it does not identify routes of exposure (inhalation, dermal?) or exposure durations (acute, chronic?) to be assessed, it does not identify metrics or measures, and it does not present an approach for representing exposure variability.

The final element of the plan for Occupational Exposures (section 2.7.2.3) is as follows:[53]

> ***"Evaluate the weight of the scientific evidence of occupational exposure data, which may include qualitative and quantitative sources of information."***
> *"During risk evaluation, EPA plans to evaluate and integrate the exposure evidence identified in the literature inventory using revised systematic review methods described in a draft systematic review protocol that EPA plans to release later this year. EPA plans to rely on the weight of the scientific evidence when evaluating and integrating occupational data. EPA plans to integrate the data using systematic review methods to assemble the relevant data, evaluate the data for quality and relevance, including strengths and limitations, followed by synthesis and integration of the evidence*." (emphasis added)

This paragraph is unclear regarding what will be assessed in the weight of evidence evaluation, and it provides very little information regarding the expected outcome and products of the occupational exposure analysis. A more useful analysis plan would outline the expected outputs of the occupational exposure analysis that will be provided in the risk evaluation. A concise statement indicating the exposure pathways and routes, exposure durations, and exposure metrics to be assessed is needed, along with indications of how uncertainty and variability will be represented (e.g., presentation of central estimates and/or upper bound estimates).

[53] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 52. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

Similar limitations are found for each major element in the analysis plan.

Physical and Chemical Properties and Environmental Fate (section 2.7.1). This section fails to identify the physical and chemical properties for which measured or modeled values are needed (perhaps this information is found elsewhere in the scope document; if so, it should be referenced in this section for clarity). It also indicates that a "a weight of the scientific evidence evaluation of physical and chemical properties and environmental fate data"[54] will be conducted but does not state the objective of evaluation and its intended output. Is the objective to obtain a single estimate for each needed parameter? Is each value intended to be a "best estimate?" Is there any accounting for uncertainty in the parameter values?

Environmental Releases (section 2.7.2.1). The final element of this section is to "*Evaluate the weight of the scientific evidence of environmental release data*."[55] The plan should explain the objective of this weight of the scientific evidence evaluation and its intended output. What are the parameters to be estimated? In what units/metrics are they expressed? Is each value intended to be a "best estimate?" Is there any accounting for uncertainty and variability in the parameter values?

Environmental Exposures (section 2.7.2.2). The final element of this section is to "*Evaluate the weight of the scientific evidence of environmental occurrence data and modeled estimates*."[56] The plan should explain the objective of this weight of the scientific evidence evaluation and its intended output. What are the parameters to be estimated? In what units/metrics are they expressed? Is each value intended to be a "best estimate?" Is there any accounting for uncertainty and variability in the parameter values?

Consumer Exposures (Section 2.7.2.4). This section does not include identification of the characteristics of the consumers of D4-containing products, which is necessary information to identify potentially exposed or susceptible subpopulations. Although the section mentions review of "*Review reasonably available population- or subpopulation-specific exposure factors and activity patterns to determine if PESS need to be further refined*,"[57] it is not clear whether this task includes determination of who the consumers are. Important questions that should be considered in the analysis plan include: Are the consumer products containing D4 used by children? What are the demographic characteristics (e.g., race/ethnicity, income) of the consumers of D4 products? Are exposure levels likely to be correlated with any demographic variables?

The consumer exposure plan also does not provide basic information about the planned assessment, such as routes of exposure (inhalation, dermal?), exposure duration (acute, chronic?), or approach to accounting for variability in exposure due to factors such as consumer product formulation, usage pattern (amount, duration and frequency of use), or exposure environment (e.g. air exchange rate).

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[54] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 47. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

[55] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 49. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

[56] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 51. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

[57] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 54. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

The final element of the Consumer Exposures plan is to "*Evaluate the weight of the scientific evidence of consumer exposure estimates based on different approaches*."[58] The plan should explain the objective of this weight of the scientific evidence evaluation and its intended output. What are the parameters to be estimated? In what units/metrics are they expressed? Is each value intended to be a "best estimate?" Is there any accounting for uncertainty and variability in the parameter values?

General Population (Section 2.7.2.5). This section indicates that "*The results of first tier analyses inform whether scenarios require more refined analysis*."[59] The expected contents of the first tier analyses are unclear, and no indication is provided of *how* their results will inform a decision regarding whether more refined analysis will be conducted, or whether variability in exposure and susceptibility across potentially exposed or susceptible subpopulations will be considered in that decision.

The section does not include identification of the characteristics (e.g. race/ethnicity, income, lifestage) of populations living in proximity to facilities releasing D4 to the environment, which is necessary information to assess risks to PESS .

The final element of the General Population plan is to "*Evaluate the weight of the scientific evidence of general population exposure estimates based on different approaches*."[60] The plan should explain the objective of this weight of the scientific evidence evaluation and its intended output. What are the parameters to be estimated? In what units/metrics are they expressed? Is each value intended to be a "best estimate?" Is there any accounting for uncertainty and variability in the parameter values?

Human Health Hazards (section 2.7.3.2). This section is very general and does not incorporate readily available information on toxicity endpoints for D4. For example, previous assessments of D4 by ECHA[61] and Health Canada[62] have identified reproductive endpoints, respiratory irritation, increased liver weight, decreased fetal body weight and decreased fetal liver weight as hazards of D4. The analysis plan should also incorporate the information on health effects studies presented in Figure 2-10 (Literature Inventory Heat Map) of the draft scope document. Similar to the other sections of the analysis plan, this section needs to identify the objectives and the expected outputs of the "weight of the scientific evidence" evaluation.

6. The approaches to dose-response assessment and risk characterization in the analysis plan needs to be clarified and expanded.

Although the information in the analysis plan regarding dose-response assessment and risk characterization for non-cancer effects is very limited, it appears that EPA plans to take the same

[58] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 54. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

[59] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 55. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

[60] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 56. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

[61] European Chemicals Agency, 2015. Annex XV Restriction Report. Proposal For A Restriction. Substance Name: Octamethylcyclotetrasiloxane. https://echa.europa.eu/documents/10162/9a53a4d9-a641-4b7b-ad58-8fec6cf26229.

[62] Health Canada, 2008. Screening Assessment for the Challenge: Octamethylcyclotetrasiloxane (D4). https://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=2481B508-1

approach that was used in the ten TSCA risk evaluations completed from June 2020 to January 2021. This approach consists of three steps: first, estimating a point of departure; second computing a margin of exposure (MOE) as the ratio of the POD to the exposure estimate; and third, comparing the calculated exposure to a "benchmark MOE" that is the product of uncertainty factors deemed appropriate for application to a particular POD, which may include factors for interspecies extrapolation, intraspecies human variability, subchronic-to-chronic exposure duration extrapolation, and LOAEL-to-NOAEL extrapolation. As explained in a previous EPA TSCA risk evaluation, an exposure MOE less than the benchmark MOE is "interpreted as human health risk," and an exposure MOE greater than the benchmark MOE "indicated negligible concerns for adverse human health effects."[63]

The MOE approach to assessment of non-cancer effects sets a "bright line" in which exposures below a specified level are assumed to pose no risk of concern, and exposures above a specified level are assumed to potentially pose some undetermined risk – with no estimate of the magnitude of risk to the exposed population. Continued use of the MOE approach in the D4 risk evaluation would not fully satisfy the requirements of TSCA to use the best available science and to assess risks to PESS, and it will not provide the most useful information for risk management decision-making in the case of an unreasonable risk determination. To meet these needs, the scope document should commit to incorporating probabilistic methods for dose-response analysis, and to use the outputs of the probabilistic methods for risk characterization. These methods will substantially improve TSCA risk evaluations by enabling EPA to quantify how population risk varies at differing levels of exposure.

Methods to quantify risks of non-cancer effects have been described by authoritative bodies such as the NAS[64] and World Health Organization[65] and demonstrated in published case studies.[66,67,68] Such methods, which provide estimates of the number of cases of disease in a population with a given level of exposure, are necessary for a complete characterization of non-cancer risk, for a complete characterization of any health inequities that may be associated with exposure to D4, and to support economic analysis of the benefits of any risk management actions that would follow an unreasonable risk determination.

In addition to incorporating probabilistic methods, additional improvements to the text concerning dose-response analysis in section 2.7.3.2, "Human Health Hazards," are needed. In particular, the text regarding dose-response analysis in item 3 is redundant and confusing. We urge EPA to make the following improvements:

- Delete the dose-response text (i.e. paragraphs 2 and 3) from item 3 as dose-response is addressed more clearly in item 4. Item 3 would then be focused on hazard identification, leaving dose-response assessment to item 4.

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[63]U.S. Environmental Protection Agency, 2020. Risk Evaluation for Trichloroethylene, p. 303. https://www.epa.gov/sites/default/files/2020-11/documents/1._risk_evaluation_for_trichloroethylene_tce_casrn_79-01-6.pdf

[64]National Research Council (US) Committee on Improving Risk Analysis Approaches Used by the U.S. EPA. Science and Decisions: Advancing Risk Assessment. Washington (DC): National Academies Press (US); 2009. PMID: 25009905.

[65]WHO/IPCS. 2014. "Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization." Geneva, Switzerland: World Health Organization; http://apps.who.int/iris/bitstream/10665/259858/1/9789241513548-eng.pdf?ua=1

[66]Ginsberg GL. Cadmium risk assessment in relation to background risk of chronic kidney disease. J Toxicol Environ Health A. 2012;75(7):374-90. doi: 10.1080/15287394.2012.670895. PMID: 22524593.

[67]Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G.. Beyond the RfD: Broad Application of a Probabilistic Approach to Improve Chemical Dose-Response Assessments for Noncancer Effects. Environmental Health Perspectives. 2018;126(6): 067009. https://doi.org/10.1289/EHP3368.

[68]Blessinger T, Davis A, Chiu WA, Stanek J, Woodall GM, Gift J, Thayer KA, Bussard D. Application of a unified probabilistic framework to the dose-response assessment of acrolein. Environ Int. 2020 Oct;143:105953. doi: 10.1016/j.envint.2020.105953.

- Some of the text deleted from item 3 could be restored under item 4 if appropriately revised. In paragraph 2, the reference to MOE should be replaced with improved methods described above. The last sentence of this paragraph, concerning "if additional information on the identified hazard endpoints are not reasonably available"[69] is unclear regarding the intended approach and should be deleted entirely.
- In paragraph 3, the initial sentences regarding mode of action and human relevance are confusing without the broader context of carcinogen hazard assessment, and should be replaced with text representing a broader perspective on evaluation of cancer hazard and selection of a cancer hazard descriptor. Move this revised paragraph to item 4.

Section 2.7.4, "Summary of Risk Approaches for Characterization," states that "*for human health risk characterization, EPA plans to integrate exposure estimates from measured and/or modeled data with hazard data to characterize risk to human health*."[70] The analysis plan lacks any indication of how this integration will be done, which is a critical omission. Based on past practice, it appears that risk characterization will consist of computing an MOE and comparing this value to a benchmark MOE.

By adopting probabilistic dose-response methods described above, EPA could substantially improve its approach to risk characterization and provide more useful information for decision-makers. We recommend combining any exposure estimates with the outputs of probabilistic dose response methods to estimate non-cancer population risks expressed as frequency of cases in the exposed population, e.g. "X cases per 1000 exposed."

Even if EPA chooses not to use our recommended approach, this section needs to explain how EPA will integrate exposure estimates with hazard data for risk characterization. It seems likely that EPA plans to use the same approach that was used in the ten risk evaluations that were completed from June 2020 to January 2021. Since it would be a simple exercise to spell out that existing approach in the draft analysis plan, the absence of any text at all regarding the approach leads to uncertainty and increased potential for adverse comments when the draft risk evaluation is subject to peer review and public comment. At a minimum, the analysis plan should disclose any approaches that EPA is considering for risk characterization.

As noted above in point # 2, it is important that the risk characterization assess aggregate exposure, accounting for the fact that the same individual may experience combinations of occupational exposures, consumer exposures and general population exposures.

Among the general statements provided in this section regarding the planned risk characterization is that it will present "*the expected risk or central estimate of risk for the PESS affected*" and "*each appropriate upper-bound or lower-bound estimate of risk*."[71] However, no indication is given of how upper- or lower-bound estimates of risk will be determined. The analysis plan needs to describe the

[69] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 58. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

[70] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 60. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

[71] US EPA. (2021). Octamethylcyclotetra-Siloxane (D4); Draft Scope of the Risk Evaluation To Be Conducted Under the Toxic Substances Control Act; Notice of Availability and Request for Comments), pp. 60. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0443-0021

nature of the uncertainty or variability to be addressed and to identify the parameters to be assessed with varying values to derive upper- and lower-bound estimates of risk.