August 3, 2020

Comments on octamethylcyclotetrasiloxane (D4): Manufacturer Requests for Risk Evaluation Under the Toxic Substances Control Act (TSCA)

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

The following comments are being submitted by the University of California, San Francisco (UCSF) Program on Reproductive Health and the Environment (PRHE). 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 manufacturer requests for EPA to conduct risk evaluations 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 an important commercial chemical that is used to make other silicone chemicals, and as an ingredient in cosmetics, hair care products and deodorants.[2,3] While the data on the health impacts of this chemical has been limited, it is sufficient enough that the UK, Canada, and ECHA have all have classified it as Persistent, Bioaccumulative, and Toxic.[4,5,6] The consensus is that D4 is dangerous for the environment, and may cause long-term adverse effects in the aquatic environment. With regard to human health, studies indicate that D4 is linked to adverse reproductive health outcomes such as a risk of impaired fertility, as D4 mimics the female hormone estrogen in laboratory animals following oral exposure to very low doses.[7]

With regard to regulations, on 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]

TSCA mandates that EPA use the "best available science"[10] to inform its decisions on chemicals, and that EPA apply the same standards to manufacturer-requested risk evaluations as required for all other evaluations.[11] However, we find that the draft risk evaluation for D4 prepared by Silicones Environmental, Health, and

[1] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Manufacturer Request for Risk Evaluation of Octamethylcyclotetrasiloxane (D4). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0004

[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] 15 USC §2625(h)

[11] 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."

Safety Center falls short on multiple methodological and scientific aspects. Thus, we strongly recommend against the use of this draft risk evaluation to inform any EPA processes regarding D4 moving forward.

Our comments address the following main issues:

1. **Should EPA proceed with the risk evaluation of D4, it should not consider nor incorporate the draft risk evaluation submitted by the Silicones Environmental, Health and Safety Center (SEHSC), which is made up of Dow Silicones Corporation, Elkem Silicones USA Corporation, Evonik Corporation, Momentive Performance Materials, Shin-Etsu Silicones of America, Inc., and Wacker Chemical Corporation, for the reasons detailed below:**
    a. **The draft risk evaluation provided by SEHSC uses EPA's TSCA systematic review method, which we have previously commented is not consistent with best scientific practices in systematic reviews.**
    b. **The reference lists presented in the manufacturer requests do not include all relevant information.**
    c. **The conclusions of the SEHSC draft risk evaluation directly contradict other regulatory agencies and the most current science on D4.**
2. **Should EPA proceed with the risk evaluation of D4, it should include all intended, known or reasonably foreseen conditions of use and the associated exposures. Failure to do so will underestimate risk, especially to potentially exposed or susceptible sub-populations.**
3. **To make a risk determination, EPA must have adequate data. EPA needs to determine the completeness of the database on D4 and siloxanes for assessment and exercise its full authorities to fill data gaps under TSCA sections 4 and 8 and make information public under section 14.**

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

Sincerely,

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DETAILED COMMENTS

1. **Should EPA proceed with the risk evaluation of D4, it should not consider nor incorporate the draft risk evaluation submitted by the Silicones Environmental, Health and Safety Center (SEHSC), which is made up of Dow Silicones Corporation, Elkem Silicones USA Corporation, Evonik Corporation, Momentive Performance Materials, Shin-Etsu Silicones of America, Inc., and Wacker Chemical Corporation, for the reasons detailed below:**

In the SEHSC request for evaluation for D4 under TSCA, the manufacturers include "…a draft risk evaluation for D4 that has been prepared in accordance with EPA's Guidance to Assist Interested Persons in Developing and Submitting Draft Risk Evaluations under the Toxic Substances Control Act, June 2017 for the Agency's consideration as provided for in TSCA § 26(l)(5)." [12] However upon review of the draft risk evaluation, it contains serious methodological flaws and draws conclusions which are not supported by current scientific evidence. If EPA proceeds with the risk evaluation of D4, it should not consider nor incorporate this draft risk evaluation.

   a. **The draft risk evaluation provided by SEHSC uses EPA's TSCA systematic review method, which we have previously commented is not consistent with best scientific practices in systematic reviews.**

The TSCA systematic review methodology is not a peer-reviewed, validated method

Within the included draft risk evaluation, SEHSC uses EPA's TSCA Method which it indicates has enabled it to identify sufficient relevant information for the manufacturer-requested risk evaluation (MRRE). We have commented extensively around the flaws in EPA's TSCA Method, which are attached in Appendix A. EPA should conduct a systematic literature review using an established, peer-reviewed method such as the National Toxicology Program's Office of Health Assessment and Translation or UCSF's Navigation Guide. [13,14] The TSCA systematic review method should not be used, as it is not peer-reviewed or validated, and EPA's Science Advisory Committee on Chemicals has raised serious concerns about it.[15]

[12] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Manufacturer Request for Risk Evaluation of Octamethylcyclotetrasiloxane (D4). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0004

[13] National Toxicology Program (2015) Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. In: U.S. Department of Health and Human Services, editor.: Office of Health Assessment and Translation, Division of National Toxicology Program, National Institute of Environmental Health Sciences.

[14] Woodruff TJ, Sutton P (2014) The Navigation Guide sytematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environmental Health Perspectives. 122(10):A283.

[15] SACC (2019) A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Peer Review for EPA Draft Risk Evaluation of C.I. Pigment Violet 29

Failure to consider financial conflicts of interest

Critically, EPA's TSCA method does not consider financial conflicts of interest as a potential source of bias in research. Financial conflicts of interest were described by the Deputy Editor (West) of JAMA in 2010, "the biggest threat to [scientific] integrity [is] financial conflicts of interest,"[16] and we cover this in detail in our comments to NAS (Appendix A, Point 6). The draft risk evaluation submitted by SEHSC includes a substantial number of studies which have been conducted by manufacturers that produce D4, and thus represent a financial conflict of interest. While in some cases the direct involvement of the manufacturer is very clear, unpublished reports conducted by the manufacturer, in others it is less so. For example, Whelan et al. (2019) has stated author affiliations with Dow (J.Kim and N.Suganuma), and in the acknowledgements states that the work was funded by Centre Européen des Silicones (CES; a trade organization respresenting the Silicone manufacturers in Europe); however despite these affiliations and funding from the industry, Whelan et al. (2019) still fails to declare any conflicts of interest.[17] If authors are affiliated with the manufacturer, and the research is funded by a group representing manufacturer and their interests, then it should be considered as a potential risk of bias. Other studies, which are funded in whole or part by a trade organization representing silicone manufacturers but fail to declare a financial conflict of interest in the manuscript are Xu et al. (2019)[18], Kozerski et al. (2014)[19], and Kim et al. (2018).[20]

b. The reference lists presented in the manufacturer requests do not include all relevant information.

The reference lists presented in the Manufacturer Request does not capture all information relevant for the risk evaluations, as the requests state these lists are limited to information relevant to the conditions of use identified in the requests. [21, 22] The manufacturer Certification, Commitment, and Contact Information forms state:

"I have either identified or am submitting all information in my possession, control, and a description of all other data known to or reasonably ascertainable by me as required for this request under this part [40 C.F.R. Part 702]." [23]

However, the draft risk evaluation submitted by SEHSC fails to include the most recent experimental and environmental fate modeling studies on D4, which demonstrate strong evidence for persistence of D4 in

[16] Rennie D. Integrity in scientific publishing. Health Serv Res. 2010;45(3):885-96. Epub 2010/03/27. doi: HESR1088 [pii] 10.1111/j.1475-6773.2010.01088.x. PubMed PMID: 20337732

[17] Whelan et al. Uncertainty and equifinality in environmental modelling of organic pollutants with specific focus on cyclic volatile methyl siloxanes. *Environ. Sci.: Processes Impacts*, 2019, 21, 1085-1098.

[18] Xu et al. Long-range transport potential and atmospheric persistence of cyclic volatile methylsiloxanes based on global measurements. *Chemosphere*, 2019, 228, 460-468.

[19] Kozerski, G. E., Xu, S., Miller, J., & Durham, J. (2014). Determination of soil-water sorption coefficients of volatile methylsiloxanes. *Environmental Toxicology and Chemistry, 33*(9), 1937-1945. doi:10.1002/etc.2640

[20] Kim et al. Predicted persistence and response times of linear and cyclic volatile methylsiloxanes in global and local environments. *Chemosphere*, 2018, 195, 325-335.

[21] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Manufacturer Request for Risk Evaluation of Octamethylcyclotetrasiloxane (D4). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0004

[22] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Possible Conditions of Use (COU) Table for Octamethylcyclotetrasiloxane (D4). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0003

[23] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Manufacturer Request for Risk Evaluation of Octamethylcyclotetrasiloxane (D4). Page 15. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0004

aquatic environments.[24, 25, 26,27,28] It is unlikely that Dow Chemicals and Dow Corning employees did not have knowledge of the Panagopoulos et al and Abrahamsson et al studies, as they are cited in several published studies including studies published by at least one co-author from Dow Chemicals or Dow Corning, such as Whelan et al. (2019),[29] Xu et al. (2019)[30] and Kim et al. (2018).[31] This lack of inclusion of relevant scientific information again calls into question the validity of the systematic review method used as it has failed to identify all relevant studies needed to conduct a rigorous evaluation of the possible harms of D4. A select list of experimental and environmental fate modeling studies missing from the SEHSC draft risk evaluation is contained in Appendix B.

EPA is required to evaluate all conditions of use under TSCA and thus the manufacturers should be submitting all information on D4 that is reasonably available to them, including previously unpublished or unsubmitted studies and data in the manufacturers' possession. Thus, the draft risk evaluation provided by SEHSC failed to incorporate all relevant information known to the parties, and specifically failed to incorporate information that may support a finding of unreasonable risk.

c. The conclusions of the SEHSC draft risk evaluation directly contradict other regulatory agencies and the most current science on D4

The SEHSC draft risk evaluation found that D4 did not present unreasonable risk of injury to human health or the environment under its conditions of use. [32,33] The draft risk evaluation also concludes that D4 has low persistence, does not biomagnify in the aquatic or terrestrial food chain, and is not toxic to humans. [34] These limited conclusions are in direct contradiction to the conclusions of other regulatory agencies in Canada, Europe and the U.K., as well as the best available science on D4.

For example, in the "possible conditions of use" document, EPA states that "This list does not constitute all the uses that may be evaluated in a risk evaluation for octamethylcyclotetra- siloxane," and lists 34 total conditions of use, the majority of which (24/34) were provided by EPA. [35] The SEHSC draft risk evaluation was based on a limited number of COUs identified by the manufacturers, which similarly limits the validity of the SEHSC draft risk evaluation conclusions. For example, when considering D4 in personal care products,

[24] Panagopoulos D. MacLeod, M. A critical assessment of the environmental fate of linear and cyclic volatile methylsiloxanes using multimedia fugacity models. *Environ. Sci.: Processes Impacts*, 2018, 20, 183-194.

[25] Abrahamsson et al. Investigating the presence and persistence of volatile methylsiloxanes in Arctic sediments. *Environ. Sci.: Processes Impacts*, 2020, 22, 908-917.

[26] Panagopoulos et al. 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.

[27] Panagopoulos et al. Evaluating the salting-out effect on the organic carbon/water partition ratios (K_{OC} and K_{DOC}) of linear and cyclic volatile methylsiloxanes: Measurements and polyparameter linear free energy relationships. *J. Chem. Eng. Data* 2016, 61, 9, 3098–3108.

[28] Panagopoulos et al. Temperature dependence of the organic carbon/water partition ratios (K_{OC}) of volatile methylsiloxanes. *Environ. Sci. Technol. Lett.* 2017, 4, 6, 240–245.

[29] Whelan et al. Uncertainty and equifinality in environmental modelling of organic pollutants with specific focus on cyclic volatile methyl siloxanes. *Environ. Sci.: Processes Impacts*, 2019, 21, 1085-1098.

[30] Xu et al. Long-range transport potential and atmospheric persistence of cyclic volatile methylsiloxanes based on global measurements. *Chemosphere*, 2019, 228, 460-468.

[31] Kim et al. Predicted persistence and response times of linear and cyclic volatile methylsiloxanes in global and local environments. *Chemosphere*, 2018, 195, 325-335.

[32] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Manufacturer Request for Risk Evaluation of Octamethylcyclotetrasiloxane (D4). Page 270. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0004

[33] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Possible Conditions of Use (COU) Table for Octamethylcyclotetrasiloxane (D4). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0003

[34] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Manufacturer Request for Risk Evaluation of Octamethylcyclotetrasiloxane (D4). Page 9. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0004

[35] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Possible Conditions of Use (COU) Table for Octamethylcyclotetrasiloxane (D4). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0003

EPA identified 3 of the 4 possible conditions of use: Incorporation into formulation, mixture, or reaction product, Processing – Repackaging), and commercial uses. While Dow Silicones Corporation et al only identified one: consumer uses. The SEHSC draft risk evaluation is incomplete in myriad ways and the conditions of use put forth by the manufacturers does not present in sufficient detail the current conditions of use and all the reasonably foreseen conditions of use. Additionally, EPA states that it "must also assess what, if any, additional conditions of use warrant inclusion within the scope of a risk evaluation for the chemical substance." [36] We recommend that EPA make available for comment all conditions of use prior to conducting its draft risk evaluation for D4.

The SEHSC draft risk evaluation makes assumptions about D4 emission sources which are not supported by the science

On page 233 of the draft risk evaluation, SEHSC states that discharge of D4 to the environment are based on the assumption that the main emissions to the environment occur from manufacturing plants.[37] While this may be reflected by the limited conditions of use that SEHSC presented, [38] it is in direct contradiction to the risk assessments conducted by Environment Canada and the UK's Environment Agency on D4, D5 and D6, which presented sufficient evidence that the main emissions of these chemicals occur from applications of personal care products and through volatilization from polydimethylsiloxane (PDMS). Additionally, the observation that the main emission of siloxanes to the environment occurs through use of personal care products is also supported by the consumption estimates given by the silicone industry.[39] Thus, assuming that D4 is mainly emitted via wastewater from manufacturing plants would greatly underestimate the amount of D4 annually released to the environment.

The SEHSC draft risk evaluation concludes that D4 is not a PBT

The conclusions from the SEHSC draft risk evaluation contradict the conclusions of major regulators. Both Environment Canada,[40,41,42] and the UK's Environment Agency[43,44,45] have concluded that D4 fulfills the REACH criteria for PBT, and the criteria for vPvB (very persistent; **very** bioaccumulative).[46] Additionally, in November 2012 the ECHA PBT Expert Group found D4 "*meets the Annex XIII criteria for identification as a*

[36] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Possible Conditions of Use (COU) Table for Octamethylcyclotetrasiloxane (D4). Pg. 1. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0003

[37] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Manufacturer Request for Risk Evaluation of Octamethylcyclotetrasiloxane (D4). Page 272. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0004

[38] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Possible Conditions of Use (COU) Table for Octamethylcyclotetrasiloxane (D4). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0003

[39] https://www.silicones.eu/

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

[41] Environment Canada, Health Canada (2008) Screening assessment for the challenge: decamethylcyclopentasiloxane (D5). CAS RN 541-02-6, Environment Canada

[42] Environment Canada, Health Canada (2008) Screening assessment for the challenge: dodecamethylcyclohexasiloxane (D6). CAS RN 540-97-6, Environment Canada

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

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

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

[46] REACH Online. **ANNEX XIII: CRITERIA FOR THE IDENTIFICATION OF PERSISTENT, BIOACCUMULATIVE AND TOXIC SUBSTANCES, AND VERY PERSISTENT AND VERY BIOACCUMULATIVE SUBSTANCES. Available:** https://reachonline.eu/reach/en/annex-xiii.html#:~:text=This%20Annex%20lays%20down%20the,and%20T%20properties%20of%20a

persistent, bioaccumulative and toxic (PBT) and very persistent very bioaccumulative (vPvB) substance and decamethylcyclopentasiloxane (D5) meets the criteria for a vPvB substance."[47]

However, the SEHSC draft risk evaluation also only utilizes a subset of the data in comparison to the aforementioned reports and therefore, fails to include critical data supporting the assertion that D4 is a PBT, despite Dow (a member of the SEHSC) being knowledgeable of such studies, evidenced by its previous citing of these studies in publication.[48,49,50]

Persistence

The SEHSC draft risk evaluation assessment on the persistence of D4 contains major flaws and disregards the most recent experimental and modeling studies on D4 and its persistence in aquatic environments.

The SEHSC dismissed the results in Panagopoulos et al. (2015)[51] on the grounds that it is an indirect measurement of the partition ratio of D4 between organic carbon and water (K_{OC}), indicating that for this reason it is "less reliable."[52] However, it is important to note that directness is not a measure of reliability and that measurements in chemistry are generally indirect measurements. For example, when measuring the concentration of a chemical in a sample one does not measure the number of molecules in a sample, but rather the effect that these molecules have on the detector of an analytical instrument, e.g., a mass spectrometer. Even when the quantity of a pure chemical is measured using a scale, it still does not represent a direct measurement (as again we don't measure the number of molecules), but rather the effect that the weight of the chemical has on the sensor of the scale. These measurements are considered valid measurements because the instruments used are calibrated, and the approaches have been validated with experimental data.

In the same sense, the measurements of K_{OC} in Panagopoulos et al. (2015) are reliable because the method was calibrated and validated using organic chemicals with well-characterized physicochemical properties, 1,4-dichlorobenzene (1,4-DCB), alpha-hexachlorocycloxehane (a-HCH) and polychlorinated biphenyls (PBCs). The study was conducted using indirect measurements due to the extreme hydrophobicity of D4, as the concentrations of D4 in the water phase of a partitioning system are so small that they cannot be determined directly using conventional analytical methods, given the analytical uncertainties. The hydrophobicity of D4 raises important questions about the measurements in the 2007 Dow Corning study,[53] around how these measurements were evaluated, given the large analytical uncertainties in measuring trace concentrations of D4, and whether contamination during the analysis of the water phase may result in higher concentrations of D4 in the water and thus lower measurements of K_{OC}. Dow Corning needs to answer these methodological questions, which could explain why their measurements are ~0.5 log units lower than reported in Panagopoulos et al. (2015). If Dow Corning underestimated the chemical K_{OC}, this

[47] ECHA. 2015. Annex XV Restriction Report: Proposal for a Restriction. D4 and D5. Health & Safety Executive: Bootle, U.K., 2015; version 1.1. European Chemicals Agency. https://echa.europa.eu/documents/10162/9a53a4d9-a641-4b7b-ad58-8fec6cf26229 (Accessed March 28, 2017)

[48] Whelan et al. Uncertainty and equifinality in environmental modelling of organic pollutants with specific focus on cyclic volatile methyl siloxanes. *Environ. Sci.: Processes Impacts*, 2019, 21, 1085-1098.

[49] Xu et al. Long-range transport potential and atmospheric persistence of cyclic volatile methylsiloxanes based on global measurements. *Chemosphere*, 2019, 228, 460-468.

[50] Kim et al. Predicted persistence and response times of linear and cyclic volatile methylsiloxanes in global and local environments. *Chemosphere*, 2018, 195, 325-335.

[51] Panagopoulos et al. 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.

[52] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Manufacturer Request for Risk Evaluation of Octamethylcyclotetrasiloxane (D4). Page 65. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0004

[53] Kozerski, G. E., Xu, S., Miller, J., & Durham, J. (2014). Determination of soil-water sorption coefficients of volatile methylsiloxanes. *Environmental Toxicology and Chemistry, 33*(9), 1937-1945. doi:10.1002/etc.2640

would lead to underestimating the persistence in the aquatic environment, given that the fate of D4 is immediately controlled by its strong affinity for organic carbon found in sediments and suspended particles in the water.

A number of fate and transport modeling studies have been published, including Krogseth et al. (2017),[54] Panagopoulos et al. (2018),[55] and Abrahamsson et al. (2020).[56] However, the SEHSC draft risk evaluation does not include any modeling studies from peer-reviewed publications which assess the persistence of D4 in the environment, and especially in the aquatic environment, which limits the conclusions that can be drawn from their assessment.[57] Before any conclusions are drawn on the persistence of siloxanes, there needs to be a systematic review of the environmental fate modeling studies in the literature. This is particularly important as Panagopoulos et al. (2018) and Abrahamsson et al. (2020) conducted extensive modeling calculations of environmental fate using measurements from both Dow Corning (2007) and Panagopoulos et al. (2015). Both studies show that the uncertainty in the measurements of K_{OC} has very important implications in calculations of persistence for D4. When using Dow Corning's measurements, D4 appears to be non-persistent. When using the Panagopoulos et al. (2015) measurements, D4 appears to be very persistent (vP), supported by the determinations from both Canada and the UK.

Furthermore, Abrahamsson et al. (2020) used experimentally determined concentrations of D4, D5 and D6 in sediments and conducted modeling calculations of persistence, comparing measurements from both Dow Corning (2007) and Panagopoulos et al. (2015) to determine which could predict D4 concentrations in sediment more accurately. The study found that Panagopoulos et al. (2015) calculations predicted the concentrations of D4 in the sediments with an error of about 1 order of magnitude, while the Dow Corning calculations underestimated the concentrations in sediment by almost 3 orders of magnitude.[58] These findings are also supported by Krogseth et al. (2017) which found that Panagopoulos et al. (2015) produced substantially more accurate predictions than Dow Corning (2007).

Thus, the SEHSC draft risk evaluation cannot be used to determine persistence because it doesn't include all the relevant data and models.

Bioaccumulation

The SEHSC draft risk evaluation collected numerous studies on the bioaccumulation and biomagnification of D4, however it failed to distinguish between the two and drew conclusions on bio**accumulation** using data from bio**magnification**.[59] While it is true that there is conflicting evidence about the potential of D4 to increase in concentration across food webs (biomagnification), there is substantial evidence suggesting that D4 accumulates in individual organisms at very high levels (bioaccumulation).[60] For example researchers

[54] Krogseth et al. Understanding of cyclic volatile methyl siloxane fate in a high latitude lake Is constrained by uncertainty in organic carbon–water partitioning. *Environ. Sci. Technol*. 2017, 51, 1, 401–409

[55] Panagopoulos D. MacLeod, M. A critical assessment of the environmental fate of linear and cyclic volatile methylsiloxanes using multimedia fugacity models. *Environ. Sci.: Processes Impacts*, 2018, 20, 183-194.

[56] Abrahamsson et al. Investigating the presence and persistence of volatile methylsiloxanes in Arctic sediments. *Environ. Sci.: Processes Impacts*, 2020, 22, 908-917.

[57] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Manufacturer Request for Risk Evaluation of Octamethylcyclotetrasiloxane (D4). Page 62. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0004

[58] Abrahamsson et al. Investigating the presence and persistence of volatile methylsiloxanes in Arctic sediments. *Environ. Sci.: Processes Impacts*, 2020, 22, 908-917.

[59] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Manufacturer Request for Risk Evaluation of Octamethylcyclotetrasiloxane (D4). Page 190. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0004

[60] Sahlin S, Ågerstrand M. (2018). Octamethylcyclotetrasiloxane (D4) EQS data overview. Available: https://www.aces.su.se/aces/wp-content/uploads/2018/10/D4-EQS-data-overview-2018.pdf

have shown that D4 was 6 times more bioaccumulative than PCB 180 in polycheates and 14 times more bioaccumulative than PCB 180 in flounder.[61]In fact, using biomagnification data to assess bioaccumulation leads to important underestimations of the potential of a chemical to accumulate in individual organisms.

This conclusion needs to be revised accordingly as the PBT criteria[62] explicitly refer to bioaccumulation and not biomagnification.

Toxicity

Reports from Environment Canada, the U.K. Environment Agency, and ECHA have provided substantial evidence that D4 is toxic in certain aquatic organisms in long-term studies with low doses.[63,64,65 66,67,68,69] While the potential of D4 to cause adverse health outcomes in humans is still unknown, D4 shows long-term toxicity in fish, long-term toxicity in Daphnia Magna and significant toxicity to invertebrates, such as sediment organisms. It is also classified as a toxic to reproduction – category 2.[70] As outlined in the PTB criteria set forth by REACH, a substance fulfills the toxicity criterion when it is toxic in either humans or other organisms. The SEHSC draft risk evaluation concludes that D4 does not pose a harm to humans

[61] Kierkegaard, A., Egmond, R. V., & Mclachlan, M. S. (2011). Cyclic Volatile Methylsiloxane Bioaccumulation in Flounder and Ragworm in the Humber Estuary. *Environmental Science & Technology, 45*(14), 5936-5942. doi:10.1021/es200707r

[62] **PTB and vPvB criteria (from REACH)**

Persistence: A substance is considered to be persistent (P) if it has a degradation half-life >60 days in marine water or >40 days in fresh or estuarine water, or >180 days in marine sediment or >120 days in freshwater or estuarine sediment or soil. A substance is considered to be very persistent (vP) if it has a half-life >60 days in marine, fresh or estuarine water, or >180 days in marine, freshwater or estuarine sediment, or soil.

Bioaccumulation: A substance is considered to be bioaccumulative (B) if it has a bioconcentration factor (BCF) >2,000 L/kg or very bioaccumulative (vB) if it has a BCF >5,000 L/kg. REACH Annex XIII also allows a weight of evidence approach.

Toxicity: A substance fulfils the toxicity criterion (T) when:

- the long term no observed effect concentration (NOEC) for marine or freshwater organisms is less than 0.01 mg/L (10 µg/L); or
- the substance is classified as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B) or toxic for reproduction (category 1A, 1B or 2); or
- there is other evidence of chronic toxicity, as defined by the classifications STOT (repeated exposure), category 1 (oral, dermal, inhalation of gases/vapours, inhalation of dust/mist/fume) or category 2 (oral, dermal, inhalation of gases/vapours, inhalation of dust/mist/fume, according to Regulation (EC) No 1272/2008.

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

[64] Environment Canada, Health Canada (2008) Screening assessment for the challenge: decamethylcyclopentasiloxane (D5). CAS RN 541-02-6, Environment Canada

[65] Environment Canada, Health Canada (2008) Screening assessment for the challenge: dodecamethylcyclohexasiloxane (D6). CAS RN 540-97-6, Environment Canada

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

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

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

[69] ECHA. 2015. Annex XV Restriction Report: Proposal for a Restriction. D4 and D5. Health & Safety Executive: Bootle, U.K., 2015; version 1.1. European Chemicals Agency. https://echa.europa.eu/documents/10162/9a53a4d9-a641-4b7b-ad58-8fec6cf26229 (Accessed March 28, 2017)

[70] ECHA. 2015. Annex XV Restriction Report: Proposal for a Restriction. D4 and D5. Health & Safety Executive: Bootle, U.K., 2015; version 1.1. European Chemicals Agency. https://echa.europa.eu/documents/10162/9a53a4d9-a641-4b7b-ad58-8fec6cf26229 (Accessed March 28, 2017)

without considering the chemical's toxicity in other organisms. It is important to clarify that using sole harm or no harm to humans as the only criterion for evaluating toxicity is misleading and not in agreement with the conditions under which substances are classified as according to the PTB criteria. Chemicals that affect organisms other than humans have been shown to have devastating effects in the ecosystem that can indirectly affect humans, e.g., DDT.

Toxic effects to aquatic organisms are sufficient to classify a substance as toxic (T) under the PBT criteria.[71]

2. **Should EPA proceed with the risk evaluation of D4, it should include all intended, known or reasonably foreseen conditions of use and the associated exposures. Failure to do so will underestimate risk, especially to potentially exposed or susceptible sub-populations.**

EPA has proposed to assess a subset of conditions of use for D4, which include the conditions of use identified by the manufacturers and others identified by EPA. [72] However, TSCA requires EPA to determine whether "the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance or mixture, or that any combination of such activities, presents an unreasonable risk of injury to health or the environment," including to potentially exposed or susceptible sub-populations.[73]

To meet this mandate, the law requires that EPA comprehensively assess all intended, known or reasonably foreseen conditions of use, and the associated exposures. This scope is necessary both for chemicals selected for risk evaluations based on manufacturer requests *and* those designated high-priority by the Agency. Failure to do this will assure that risk will be underestimated, including for potentially exposed and susceptible subpopulations.

To accurately account for real-life exposures, EPA needs to aggregate exposures across all known pathways. EPA has described the concept of assessing aggregate exposures as "the risk cup," where every use of a chemical contributes to filling the cup.[74] The Agency can only determine if risks exceed levels of concern, that is whether the risk cup is full or overflowing, by adding together all contributing exposures. However, if known chemical uses and exposures are ignored such as the use of personal care products which are not accounted for in the SEHSC assessment (see Point 1), the cup levels will be an underestimate of the true risk posed, suggesting that risks are below levels of concern when in reality the cup might be full or overflowing, indicating an unreasonable risk that warrants action. We have previously submitted detailed comments to EPA on this topic.[75]

3. **To make a risk determination, EPA must have adequate data. EPA needs to determine the completeness of the database on D4 and siloxanes for assessment and exercise its full authorities to fill data gaps under TSCA sections 4 and 8 and make information public under section 14.**

[71] REACH Online. **ANNEX XIII: CRITERIA FOR THE IDENTIFICATION OF PERSISTENT, BIOACCUMULATIVE AND TOXIC SUBSTANCES, AND VERY PERSISTENT AND VERY BIOACCUMULATIVE SUBSTANCES. Available:** https://reachonline.eu/reach/en/annex-xiii.html#:~:text=This%20Annex%20lays%20down%20the,and%20T%20properties%20of%20a

[72] US EPA. (2020). Octamethylcyclotetrasiloxane (D4); TSCA Review. Possible Conditions of Use (COU) Table for Octamethylcyclotetrasiloxane (D4). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0443-0003

[73] 15 USC §2605(b)

[74] US EPA (January 31, 1997) PRN 97-1: Agency Actions under the Requirements of the Food Quality Protection Act. Available: https://www.epa.gov/pesticide-registration/prn-97-1-agency-actions-under-requirements-food-quality-protection-act#risk

[75] US EPA. (2020). Phosphoric acid, triphenyl ester (TPP); TSCA Review. Comment submitted by Swati Rayasam, Science Associate, Science and Policy, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0458-0032

TSCA statute[76] and regulation[77] require that EPA has adequate data on chemicals to inform its risk evaluations. Regulation also requires the evaluation of "relevant" potential human and environmental hazards.[78]

Certain health hazards are specifically designated in TSCA, indicating that Congress expressly recognized these types of health effects could present an unreasonable risk, and envisioned that EPA should assess them: "cancer/ carcinogenesis, mutagenesis/ gene mutation, teratogenesis, behavioral disorders, and birth defects."[79] To assess the sufficiency/ adequacy of the data on D4 for assessment, EPA should compare the completeness of the database on each chemical to existing lists of traits deemed important to assess for chemical safety. Additionally, EPA must assess the completeness of the database regarding information needed to conduct a cumulative assessment.

For the existing list of traits deemed important to assess for chemical safety, we recommend as a starting point the health hazard dataset needed for EPA's Design for the Environment (DfE) program to conduct an alternatives assessment, which is similar to the widely used chemical assessment protocol GreenScreen. [80,81] The dataset includes the following health endpoints:

1. Acute mammalian toxicity
    a. Oral
    b. Dermal
    c. Inhalation
2. Respiratory sensitization
3. Skin sensitization
4. Eye irritation/ corrosivity
5. Skin irritation/ corrosivity
6. Carcinogenicity
7. Mutagenicity/ genotoxicity
8. Reproductive and developmental toxicity
9. Developmental neurotoxicity
10. Neurotoxicity
11. Repeated dose toxicity
12. Endocrine activity

If EPA proceeds, it should describe the key areas (hazard and exposure) where data is lacking for the chemical and for mixtures, and issue orders or rules pursuant to TSCA Section 4 and/ or Section 8 to require manufacturers to develop or submit these data. Section 4 test orders should be focused on the most relevant test models, exposure pathways, health outcomes, and target populations (including any vulnerable or sensitive populations) anticipated to support the generation of high-quality and relevant evidence to support timely decision-making.

[76] 15 USC §2601 (b)(1)
[77] 40 CFR § 702.41 (b)
[78] 40 CFR § 702.41 (d)(3)
[79] 15 USC §2603 (b)(2)(A); 15 USC §2603 (e); 15 USC §2605 (b)(2)(D)
[80] US EPA (2011) Design for the Environment Alternatives Assessment Criteria for Hazard Evaluation. Available: https://www.epa.gov/sites/production/files/2014-01/documents/aa_criteria_v2.pdf
[81] Clean Production Action (2018) GreenScreen for Safer Chemicals. Available: https://www.greenscreenchemicals.org/images/ee_images/uploads/resources/GS_TwoPager_July2018.pdf

EPA should also make the data developed or submitted under these rules or orders publicly available. TSCA section 14 clearly states that health and safety studies are not confidential business information (CBI) and thus are not protected from disclosure. EPA should also provide a public summary characterizing the data and its completeness for each chemical and relevant mixtures.

Appendix A: NAS Comments

Appendix B: Relevant Studies not included in SEHSC DRE