March 10, 2021

Paul Mercer, Commissioner
Kerri Malinowski
Maine Department of Environmental Protection
17 State House Station
Augusta, Maine 04333-0017

Subject: Comments on Maine Draft Food Contact Chemicals of High Concern Criteria Documentation (Maine Law 32 MRSA 1742(1))

Dear Commissioner Mercer and Ms. Malinowski:

The Silicones Environmental, Health, and Safety Center (SEHSC) of the American Chemistry Council[1] ("ACC") or the "Council") appreciates the opportunity to comment on the Maine Department of Environmental Protection (DEP) draft Food Contact Chemicals of High Concern (CHC) list published on February 8, 2021, as provided for under the *Maine Act To Protect the Environment and Public Health by Further Reducing Toxic Chemicals in Packaging* (32 MRSA §§1731-1747).

The draft food contact chemicals of high concern list includes octamethylcyclotetrasiloxane (D4 – CAS# 556-67-2) which the SEHSC believes should not be included since it does not meet the **criteria of strong credible scientific evidence on toxicity or exposure** stipulated by the statute.

D4 is an intermediate for silicone polymers and food contact exposure is low

D4 is an intermediate in the manufacturing process of silicone polymers. Silicone polymers used in food contact applications are regulated under the FDA. An FDA safety evaluation is required prior to substances being approved as food contact agents. Numerous food packaging materials which include siloxanes, such as D4, have been approved as food contact materials by FDA. D4 is not directly added to any food contact materials and studies show that that the levels that are found in food contact materials are in low concentrations with "very limited migration"[2]. This indicates the actual exposure to D4 from food contact materials would be low.

D4 does not meet strong credible scientific evidence for CHC toxicity criteria

Per 32 MRSA 1742, a chemical must meet three criteria to qualify for potential inclusion in the Maine Food Contact Chemicals of High Concern list:

[1] ACC is a national trade association representing companies engaged in the business of chemistry. The Council's mission is to advocate on behalf of its members to foster innovation in manufacturing, high-tech jobs, and to enhance safety through the products of chemistry and investment in research. The Council is committed to sustainable development by fostering progress in our economy, environment and society.

[2] Kai Zhang, Jon W. Wong, Timothy H. Begley, Douglas G. Hayward & William Limm (2012) Determination of siloxanes in silicone products and potential migration to milk, formula and liquid simulants, Food Additives & Contaminants: Part A, 29:8, 1311-1321, DOI: 10.1080/19440049.2012.684891

1) The chemical is included on the list of chemicals of concern published by the department in accordance with Title 38, section 1693 or the chemical has been identified by an authoritative governmental entity on the basis of credible scientific evidence as being: a carcinogen, a reproductive or developmental toxicant or an endocrine disruptor; persistent, bioaccumulative and toxic; or very persistent and very bioaccumulative.

2) The department determines that there is strong credible scientific evidence that the chemical is a reproductive or developmental toxicant, endocrine disruptor or human carcinogen; and

3) The department determines that there is strong credible scientific evidence that the chemical meets one or more of the following additional criteria: The chemical has been found through biomonitoring studies to be present in human blood, human breast milk, human urine or other human bodily tissues or fluids; the chemical has been found through sampling and analysis to be present in a food or beverage product; or the chemical has been added to or is present in a food package.

"D4 met the criteria to be listed on Maine's Chemicals of High Concern due to its Category 1 Endocrine Disruptor classification by the European Union[3]."

There are two reasons why D4 does not meet the criteria for an ED as stated:

1. **Lack of reliable ED lists:** The EU list cited is solely a screening list, not a hazard classification. The Maine DEP recognized the limitations of this list as part of its triennial documentation update for the CHC list and stated that this EU database "did not use a weight-of-evidence approach to classify potential endocrine disrupting chemicals." The MECDC also stated that "short of an extensive chemical-by-chemical review for potential endocrine disrupting health effects, there remains a deficiency in the CHC selection process regarding identification of endocrine disrupting chemicals." [4]

   The title of the EU list of endocrine disruptors to which the Maine DEP refers is misleading – it is not a list of known endocrine disruptors. Rather the EU list is a proposed candidate list of chemicals for possible further evaluation. Maine DEP further notes that "For endocrine disrupting status, [Maine] relied on the only authoritative federal or international governmental database available that categorically classifies endocrine disrupting chemicals, the EU endocrine disruptor database. While it was not a formal weight-of-evidence approach, chemicals that were classified as Category 1 endocrine disruptors were included as potential CHCs largely because the EU endocrine disrupting list is the only authoritative federal or international governmental database available to identify potential endocrine-disrupting chemicals."[5] SEHSC agrees with DEP's characterization of the EU ED list and would encourage Maine to not consider it as a basis for identifying endocrine disruptors.

[3] Peterson, G., Rasmussen, D., Gustavson, K. (2007). Revised Report to European Commission DG Environment. Study on enhancing the Endocrine Disrupter priority list with a focus on low production volume chemicals. May 2007. ENV.D.4/ETU/2005/0028r.

[4] Section 4.2.3 of Maine CDC Chemical of High Concern Triennial Update Documentation https://www1.maine.gov/dep/safechem/childrens-products/highconcern/documents/3%20Year%20CHC%202015%20Update%20Documentation%20FINAL%20%2007.21.15.pdf).

[5] Section 4.2.3 of Maine CDC Chemical of High Concern Triennial Update Documentation https://www1.maine.gov/dep/safechem/childrens-products/highconcern/documents/3%20Year%20CHC%202015%20Update%20Documentation%20FINAL%20%2007.21.15.pdf).

In summary, there is no regulatory determination in the European Union that designates D4 as an endocrine disruptor. To date, D4 has not been proposed as an endocrine disruptor in a formal regulatory process, neither by any European Member State nor the European Commission. The EU list is a proposed candidate list of chemicals for further evaluation and should not be used as a hazard classification.

2. **Extensive research provides strong credible evidence that D4 is not an endocrine disruptor:** The silicone industry has conducted a robust research program that provides evidence that the reproductive effects seen following D4 exposure are rodent specific[6], [7] and more recent research suggesting the effects are secondary to high dose non-specific toxicity, and not a result of an endocrine mode of action, which according to EU guidance[8] indicates that a substance should NOT be considered an endocrine disruptor.

    - The World Health Organization (WHO) defines an endocrine disrupting chemical as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations." The key point to remember is that endocrine disruption, by definition, must involve endocrine activity that causes adverse health outcomes. Many lists of so-called "endocrine disruptors" are not based on identifying a causal link between an endocrine mode of action and an adverse effect.

    - Yet extensive scientific research indicates that D4 will not produce effects in humans via the endocrine system.[9,10,11,12]
        - In sub-chronic and chronic animal studies that examine the potential for estrogenic effects, the pattern of effects induced by D4 does not resemble the pattern produced by estrogens. [13]
        - The available data suggest that the mechanisms of action by which D4 affects reproduction and produces benign uterine tumors in high-dose rat experiments are specific to rats and would not occur in humans.[14] [15]

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[6] [6] Quinn, A.L., Dalu, A., Meeker, L.S., Jean, P.A., Meeks, R.G., Crissman, J.W., Gallavan, R.H., Jr., Plotzke, K.P., 2007b. Effects of octamethylcyclotetrasiloxane (D4) on the luteinizing hormone (LH) surge and levels of various reproductive hormones in female Sprague-Dawley rats. Reprod Toxicol **23**, 532-540.

[7] Plant, T. 2012. A comparison of the neuroendocrine mechanisms underlying the initiation of the preovulatory LH surve in the human, Old World monkey and rodent. *Frontiers in Neuroendocrinology, 33*:160-168.

[8] *Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009*

[9] McKim JM, Wilga PC, Breslin WJ, Plotzke KP, Gallavan RH, Meeks RG. Potential estrogenic and antiestrogenic activity of the cyclic siloxane octamethylcyclotetrasiloxane (D4) and the linear siloxane hexamethyldisiloxane (HMDS) in immature rats using the uterotrophic assay. Toxicol Sci. 2001;63:37-46.

[10]Quinn AL, Regan JM, Tobin JM, Marinik BJ, McMahon JM, McNett DA, Sushynski CM, Crofoot SD, Jean PA, Plotzke KP. In vitro and in vivo evaluation of the estrogenic, androgenic, and progestagenic potential of two cyclic siloxanes. Toxicol Sci. 2007;96:145-153.

[11] He B, Rhodes-Brower S, Miller MR, et al. 2003. Octamethylcyclotetrasiloxane exhibits estrogenic activity in mice via ERalpha. Toxicol Appl Pharmacol. 192:254-261.

[12] Lee D, Ahn C, An BS, Jeung EB (2015) Induction of the estrogenic marker calbindn-dgk by octamethylcyclotetrasiloxane. Int J Environ Res Public Health

[13] Franzen, A., Greene, T., Van Landingham, C. and Gentry, R., 2017. Toxicology of octamethylcyclotetrasiloxane (D 4). *Toxicology Letters*, 279, pp.2-22.

[14] Quinn, A.L., Dalu, A., Meeker, L.S., Jean, P.A., Meeks, R.G., Crissman, J.W., Gallavan, R.H., Jr., Plotzke, K.P., 2007b. Effects of octamethylcyclotetrasiloxane (D4) on the luteinizing hormone (LH) surge and levels of various reproductive hormones in female Sprague-Dawley rats. Reprod Toxicol **23**, 532-540.

[15] Plant, T. 2012. A comparison of the neuroendocrine mechanisms underlying the initiation of the preovulatory LH surve in the human, Old World monkey and rodent. *Frontiers in Neuroendocrinology, 33*:160-168.

    - The doses used in the animal experiments were thousands of times higher than those to which humans could be exposed, producing stress-responses specific to rodents due to nonspecific toxicity.
- Claims of endocrine activity are based on the results of screening-level assays conducted with D4[8, 9,10,11].
    - D4 exhibited insufficient activity in all assays to affect the human endocrine system.[8,9,10, 11,18]
    - D4 shows no potential to interact with other hormonal pathways based on results of screening assays, which probe potential endocrine mechanisms of action[16].
    - The potency of D4 was far lower than many naturally occurring materials that are also "triggered" by these screening assays. [17]
        - Merely producing a response in these screening assays does not indicate that a substance will act by that mode of action in an intact organism or cause adverse endocrine effects in people or the environment. Instead, one must consider the potency with which a chemical produces the response in a screening assay. [18]
        - Many common substances considered to be "safe", such as chemicals naturally occurring in our diet (e.g., genistein in soybeans and other plants), cholecalciferol (vitamin D), and intermediates of natural human metabolism are much more potent than D4 in producing a response in these same screening assays. For example, the potency of D4 detected in screening-level assays is hundreds of thousands of times weaker than naturally occurring estrogen and up to 200 times weaker than natural plant estrogens, such as those found in soy.[18]
        - Exposures to many of these natural, ubiquitous substances that are also "triggered" by the screening assays are 100 to 1000 times greater than potential exposures to D4.

In addition, a quantitative expert weight-of-evidence assessment of the confidence in modes-of-action concluded that the estrogen mode-of-action cannot be supported[19].

In summary, the available evidence indicates that D4 lacks the potential for endocrine activity in humans or the environment. The silicone industry believes that D4, as used, is safe for humans and the environment.

"Suspected of damaging human fertility, D4 is also classified as a Category 2 Reproductive Toxicant by the European Union.[20]"

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[16] Quinn AL, Regan JM, Tobin JM, Marinik BJ, McMahon JM, McNett DA, Sushynski CM, Crofoot SD, Jean PA, Plotzke KP. In vitro and in vivo evaluation of the estrogenic, androgenic, and progestagenic potential of two cyclic siloxanes. Toxicol Sci. 2007;96:145-153.

[17] McKim JM, Wilga PC, Breslin WJ, Plotzke KP, Gallavan RH, Meeks RG. Potential estrogenic and antiestrogenic activity of the cyclic siloxane octamethylcyclotetrasiloxane (D4) and the linear siloxane hexamethyldisiloxane (HMDS) in immature rats using the uterotrophic assay. Toxicol Sci. 2001;63:37-46.

[18] Borgert CJ, Matthews JC, Baker SP. 2018. Human-relevant potency threshold (HRPT) for ERα agonism. *Arch Toxicol*. 92: 1685-1702

[19] Dekant, W., Bridges, J., Scialli, A.. 2017. A quantitative weight of evidence assessment of confidence in modes-of-action and their human relevance. *Reg Tox Pharm, 90*:51-71.

[20] European Union Regulation No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures.

The classification as a Category 2 Reproductive Toxicant was done by the silicone industry out of an abundance of caution at the early stages of health and environmental research of siloxanes. Since then, extensive research demonstrates that these effects are animal specific and not relevant to humans[21,22,23,24,].

Decades of extensive research, testing and use provide clear scientific evidence that occupational, consumer and environmental exposures to D4 are safe. Human health risk assessments conducted for D4 by the EU Scientific Committee on Consumer Safety (SCCS)[25], the US Cosmetic Ingredient Review (CIR) Expert Panel[26], the Occupational Alliance for Risk Science-Workplace Environment Exposure Limits (OARS-WEEL)[27], the Australian government[28], Health Canada[29] the UK Environment Agency[30] and a peer reviewed global human health risk assessment [31] all conclude that D4 does not pose a risk to humans.

Combined with the nonspecific toxicity research program currently underway, SEHSC believes there is an abundance of strong, credible evidence that D4 is not a reproductive hazard for humans.

D4 does not meet strong credible scientific evidence for CHC exposure criteria

Identification of CHC requires that the chemical is on the COC list and meets additional toxicity and exposure criteria as defined by statute. The exposure criteria are defined as **strong credible scientific evidence** that the chemical meets one or more of the following exposure-based criteria:

- found through biomonitoring studies to be present in human blood, human breast milk, human urine, or other human bodily tissues or fluids;
- found through sampling and analysis to be present in a food or beverage product; or
- has been added to or is present in a food package.

[21] Quinn, A.L., Dalu, A., Meeker, L.S., Jean, P.A., Meeks, R.G., Crissman, J.W., Gallavan, R.H., Jr., Plotzke, K.P., 2007b. Effects of octamethylcyclotetrasiloxane (D4) on the luteinizing hormone (LH) surge and levels of various reproductive hormones in female Sprague-Dawley rats. Reprod Toxicol **23**, 532-540.

[22] Plant, T. 2012. A comparison of the neuroendocrine mechanisms underlying the initiation of the preovulatory LH surve in the human, Old World monkey and rodent. *Frontiers in Neuroendocrinology, 33*:160-168.

[23] Franzen, A., Greene, T., Van Landingham, C. and Gentry, R., 2017. Toxicology of octamethylcyclotetrasiloxane (D 4). *Toxicology Letters*, 279, pp.2-22.

[24] [24] Klaunig, J.E., Dekant, W., Plotzke, K., Scialli, A.R.2016. Biological relevance of decamethylcyclopentasiloxane (D5) induced rat uterine endometrial adenocarcinoma tumorigenesis: Mode of action and relevance to humans. *Reg Tox Pharm, 74*:S44-S56

[25] *Scientific Committee on Consumer Safety (SCCS) OPINION ON Cyclomethicone Octamethylcyclotetrasiloxane (Cyclotetrasiloxane, D4) and Decamethylcyclopentasiloxane (Cyclopentasiloxane, D5) 2010.*

[26] *Johnson, W., Bergfeld, W.F., Belsito, D.V., Hill, R.A., Klaasseen, C.D., Liebler, D.C., Marks Jr., J.G., Shank, R.C., Slaga, T.J., Snyder, P.W., Andersen, F.A. Safety Assessment of Cyclomethicone, Cyclotetrasiloxane, Cyclopentasiloxane, Cyclohexasiloxane, and Cycloheptasiloxane. International Journal of Toxicology, 30(3):1495-2275.*

[27] *http://www.tera.org/OARS/D4%20OARS%20WEEL%20FINAL.pdf*

[28] *https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=2031#cas-A_556-67-2*

[29] *Chemical Substances website.*

[30] *UK Environmental Agency. 2009. Environmental Risk Assessment Report: Octamethylcyclotetrasiloxane – Using Science to Create a Better Place. Further copies of this report are available from: The Environment Agency's National Customer Contact Centre by emailing enquiries@environment-agency.gov.uk or by telephoning 08708 506506.*

[31] Gentry, R., Franzen, A., Van Landingham, C., Greene, T. and Plotzke, K., 2017. A global human health risk assessment for octamethylcyclotetrasiloxane (D4). *Toxicology Letters*, 279, pp.23-41.

"Separate studies of European adults found D4 to be present in human blood[32,33]"

Biomonitoring only measures the detectable levels of a substance in a specific body tissue or fluid at a given time. It does not provide information about sources of exposure, how long the substance has been in the body, or the potential health effects, if any, associated with such exposure.

The biomonitoring example studies provided are from small sample size populations (40-100 people) in Germany and Norway. Even with limited sampling sizes, both studies noted that there was variable detection frequencies (18-85%) of D4 in blood plasma and particularly for the German study, "low exposure to cVMS" since the "maximum concentrations were much lower than the concentrations of the control group". The Norway study also noted, "Our results, compared to the limit of quantification (LOQ), suggest that for women in Norway the risk of internal exposure to cVMS is low."

Presence in human blood at any given moment does not indicate concerning exposure, especially by a minor route like food contact materials. Extensive data on D4 exposure by all routes demonstrates minimal absorption and if absorbed, a full understanding of the behavior inside of the body indicates that D4 is quickly eliminated by exhalation in breath or metabolized and eliminated in urine learning to minimal internal exposure under intended conditions of use[34] [35] [36] [37].

SEHSC urges the DEP to exercise the discretion afforded by the statute and list only those substances where a listing would provide a benefit to public health.

The criteria identified in the statute for Maine's Food Contact CHC list are intended to identify candidate chemicals to consider for inclusion. DEP is not required to list all substances that meet the criteria. DEP also should consider completed human health evaluations that are developed by authoritative governmental entities, when they are available, to determine if a substance warrants inclusion. Both Australia and Canada have completed regulatory evaluations for D4 which concluded that it does not pose a risk to human health. These regulatory evaluations included consideration of reproductive effects, endocrine impacts, and carcinogenicity.

The human health hazards considered in these evaluations included developmental, reproductive, and endocrine effects. As a consequence of its regulatory evaluation of D4, Canada concluded that D4 "is not entering the environment in a quantity or concentration or

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32 Hanssen, L., Warner, N., Braathen, T., Odland, J.O., Lund, E., Nieboer, E., Sandanger, T.M. (2013). "Plasma concentrations of cyclic volatile methylsiloxanes (cVMS) in pregnant and prostmenopausal Norwegian women and self-reported use of personal care products." Environment International 51, 82-87.

33 Fromme, H., Cequier, E., Kim, J.T., Hanssen, L., Hilger, B., Thomsen, C., Chang, Y.S., Volkel, W. (2015). "Persistent and emerging pollutants in the blood of German adults: Occurrence of dechloranes, polychlorinated naphthalenes, and siloxanes." Environment International 85, 292-298.

[34] Franzen, A., Greene, T., Van Landingham, C. and Gentry, R., 2017. Toxicology of octamethylcyclotetrasiloxane (D 4). *Toxicology Letters*, 279, pp.2-22.

[35] Domoradzki, J., Sushynski, C., Sushynski, J., McNett, D., Van Landingham, C. and Plotzke, K., 2017. Metabolism and disposition of [14 C]-methylcyclosiloxanes in rats. *Toxicology Letters*, 279, pp.98-114.

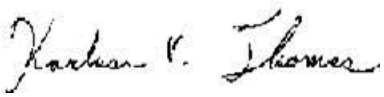
[36] Campbell, J., Andersen, M., Van Landingham, C., Gentry, R., Jensen, E., Domoradzki, J. and Clewell, H., 2017. Refinement of the oral exposure description in the cyclic siloxane PBPK model for rats and humans: Implications for exposure assessment. *Toxicology Letters*, 279, pp.125-135.

[37] McMullin, T. S., Yang, Y., Campbell, J., Clewell, H. J., Plotzke, K. P. and Andersen, M. E. Regulatory Toxicology and Pharmacology Volume 74, Supplement, February 2016, Pages S1-S13

under conditions that constitute or may constitute a danger in Canada to human life or health". The Australian Department of Health also reached a similar conclusion for D4 ("…the public risk from this chemical is not considered to be unreasonable"). These conclusions reached by authoritative governmental entities provide sufficient support for excluding D4 from the Maine Food Contact CHC listing. The inclusion of chemicals on Maine's Food Contact CHC list which do not present a risk to human health provides no benefit for public safety and is inconsistent with the implicit goal of Maine's Toxic Chemicals in Food Packaging law which is to reduce the toxicity of packaging and packaging waste.

SEHSC appreciates your consideration of our request to remove D4 from the draft food contact CHC list and we would welcome an opportunity to meet with you to discuss these comments in more detail.

Sincerely,



Karluss Thomas
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