CHARGE to the TOXIC SUBSTANCES CONTROL ACT (TSCA) SCIENCE ADVISORY COMMITTEE ON CHEMICALS (SACC)

Peer Review of Draft Risk Evaluation of D4 and Technical Support Documents

BACKGROUND:

On March 19, 2020, EPA received a manufacturer request for a risk evaluation of Octamethylcyclotetrasiloxane (Cyclotetrasiloxane, 2,2,4,4,6,6,8,8-octamethyl-), also known as D4 (CASRN 556-67-2), from Dow Silicones Corporation, Elkem Silicones USA Corporation, Evonik Corporation, Momentive Performance Materials, Shin-Etsu Silicones of America, Inc., and Wacker Chemical Corporation through the American Chemistry Council's (ACC's) Silicones Environmental, Health, and Safety Center (SEHSC). EPA accepted this request and has prepared a draft risk evaluation for D4. EPA used reasonably available data and information sources including: 1) the SEHSC manufacturer requested risk evaluation (MRRE) submission; 2) EPA's systematic review; 3) public comments; and 4) the D4 Environmental Monitoring Final Report (EPA-HQ-OPPT-2012-0209) established pursuant to the Enforceable Consent Agreement in 2014. Specifically, the D4 Environmental Monitoring Final Report was developed to support a scientifically robust environmental risk assessment for D4 by providing environmental monitoring data for several types of aquatic media and biota.

EPA is submitting the draft risk evaluation of D4 and associated technical support documents for external peer review. The draft risk evaluation includes analyses of physical and chemical properties, environmental hazard and risk, the fate and transport in the environment, releases to the environment, environmental exposure, exposure to workers, consumers, and the general population, including potentially exposed susceptible subpopulations, and human health hazard and risk characterization for workers, consumers and the general population.

EPA is not developing charge questions for all aspects of the risk evaluation but is instead focusing its charge to the SACC on specific scientific areas that need peer review. Many of the methods and analyses used in this risk evaluation are not novel and have been reviewed as part of tools and approaches used in various agency work products or in previous TSCA assessments.

EPA is requesting a focused panel discussion and feedback on novel approaches, unique exposure analyses and other calculations, and the selection of key hazard endpoints for D4.

Evaluation and use of the D4 physiologically based pharmacokinetic (PBPK) model: A PBPK model updated by Campbell et al. (2023) was used in the D4 human health risk assessment using toxicokinetic and metabolism information in rodents and humans to estimate human equivalent doses. EPA solicits input from the SACC on the PBPK model and associated outputs related to internal dosimetry, animal to human extrapolation, and point of departure derivation. EPA is soliciting input on its proposed use of the PBPK model for all routes of exposure (inhalation, oral, and dermal routes) and multiple exposure durations for non-pregnant adults.

Identification of hazards relevant to human health risk assessment: D4 exposure in laboratory animals has been shown to result in female reproductive and respiratory irritation effects. EPA is soliciting input from the SACC on the proposed hazards and points of departure (PODs) relevant for oral, dermal, and inhalation risk assessment.

Handling of uncertainties associated with exposure and release assessments: Tools and approaches used for exposure and release assessments have previously been peer reviewed. EPA seeks input on the agency's interpretation of monitoring samples that are outside the calibration curve and production volume assumptions used as the basis for release estimates.

Bioaccumulation, bioconcentration, biomagnification, and potential trophic transfer are key scientific areas for the risk evaluation of D4: Bioconcentration factor (BCF) and bioaccumulation (BAF) data for D4 indicate that D4 has high bioaccumulation potential. However, the empirical evidence from laboratory and field studies suggests low potential for biomagnification and trophic magnification of D4; trophic dilution is more likely. The divergence between bioaccumulation potential (BCF and BAF) and biomagnification potential (biomagnification factor [BMF] and trophic magnification factor [TMF]) may be explained by differences in which exposure route(s) are represented by each of these metrics, as well as differences in subsequent biotransformation rates. For example, D4 biotransformation occurs much more rapidly in the gut than in somatic/carcass tissues. As a result, accumulation primarily from the dietary route (*i.e.,* BMF and TMF) shows D4 dilution. EPA solicits input and comment on EPA's interpretation of the bioaccumulation metric data landscape and the preliminary conclusions that D4 is likely to bioaccumulate in organisms, but not magnify across trophic levels, especially considering inherent uncertainties associated with quantification of D4 in media and biota from field studies, as well as differences in exposure route control between laboratory- and field-measured metrics.

Human fish consumption for the general population and potentially exposed or susceptible subpopulations: A BAF is typically preferred when estimating human exposure to a chemical from fish ingestion because it considers the animal's uptake of the chemical from both diet and the water column. EPA is seeking input and comment on the use of a BCF in lieu of BAF to estimate D4 concentrations in fish tissue and evaluate human exposure through fish ingestion.

Identification of hazards relevant to ecological risk assessment: EPA evaluated environmental hazard endpoints associated with D4 and dimethylsilanediol (DMSD) exposure. DMSD is the terminal degradation product of D4 and is expected to persist in the aqueous environment. EPA is soliciting input and comment on the hazard database for D4 and DMSD.

CHARGE QUESTIONS:

Charge Question 1. Use of the D4 PBPK Model

Section 3.5 of the *Draft Human Health Hazard Assessment for Octamethylcyclotetrasiloxane (D4)* and supplemental files such as the *Draft PBPK Model Results for Octamethylcyclotetrasiloxane (D4)* and the *Draft PBPK Model Description and Review for Octamethylcyclotetrasiloxane (D4)* detail the 2023 D4 PBPK model to allow for route-to-route and interspecies extrapolation of the point of departure (POD) in addition to POD extrapolation for relevant exposure durations in humans.

1a. Please describe the extent to which the model code and equations reasonably perform with the input parameters to predict the model outputs.

1b. Please comment on the strengths and uncertainties of the PBPK model and associated outputs related to internal dosimetry, animal-to-human extrapolation, route to route extrapolation, duration extrapolation, and POD derivation.

1c. D4 is a volatile chemical and available information suggests that dermal absorption of D4 is limited. As described in Section 5.1.1.3 of the *Draft Risk Evaluation for*

Octamethylcyclotetrasiloxane (D4), and in the *Draft PBPK Model Description and Review*, the PBPK model incorporates several parameters that reflect available human and in vitro information on evaporation and absorption. Please comment specifically on the strengths and uncertainties of input data and assumptions made to account for evaporation and dermal absorption for derivation of a dermal POD.

1d. The PBPK model is designed to model exposures in non-pregnant adults based on adult toxicokinetic parameters. The PODs derived in the PBPK model are also applied to assess risks to children in some consumer and general population exposure scenarios, as described in Section 5.3.3 and 5.3.4 of the *Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4)*. Please comment on the strengths and uncertainties of applying the PODs derived using the model for children in the D4 risk evaluation.

Charge Question 2. Human Health Hazard Assessment

D4 exposure in laboratory animals has been shown to result in female reproductive and respiratory irritation effects.

2a. Within Section 4.1 of the *Draft Human Health Hazard Assessment for Octamethylcyclotetrasiloxane (D4)* EPA identified decreased live litter size following inhalation exposure to D4 in a two-generation reproductive toxicity study as the primary basis for POD derivation. Please comment on EPA's selection of hazard endpoints and studies to support POD derivation.

2b. Section 4.1.2 of the *Draft Human Health Hazard Assessment for Octamethylcyclotetrasiloxane (D4)* details that D4 vapor exposures have historically been used to conduct inhalation toxicity studies in animals. Observations in earlier D4 range-finding studies indicate that aerosol formation appears to occur at certain high temperatures. Although some D4 COUs may generate aerosols, especially in the workplace, vapor exposure would still be expected. Aerosol formation exposure may also present local respiratory effects. Given our limited understanding of the hazard associated with aerosols for D4 and uncertainty on the extent to which aerosols are formed at lower vapor concentrations, please comment on the strengths and uncertainties of EPA's hazard identification for inhalation exposure to D4 and the relevance of available hazard information for human aerosol exposures.

2c. Section 4.2 and Appendix B of the *Draft Human Health Hazard Assessment for Octamethylcyclotetrasiloxane (D4)* present details of the dose-response analysis. Please comment on the strengths and uncertainties related to EPA's dose-response analysis and BMR selection.

Charge Question 3. Use of CDR Production Volume for the Environmental Release Assessment

In the *Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4)*, occupational exposure scenarios (OESs) for each release have been modeled with inputs from Chemical Data Reporting (CDR), Generic Scenarios (GSs), Conceptual Site Models, and Emission Scenario Documents (ESDs). Section 1.1.1 of the *Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4)* details that EPA understands values reported in 2020 to CDR to be most representative of current conditions and EPA has identified the upper-bound PV of 500,000,000 lb per year from the 2020 CDR as an appropriate basis for screening analysis in this assessment. Please comment on EPA's reliance on the high end of the CDR-reported

range as the basis for screening level assessments and the midpoint of the CDR-reported range as the basis for refined assessments.

Charge Question 4. Number of Release Days for Modeled Environmental Releases

Section 2.3.3 of the *Draft Environmental Release and Occupational Exposure Assessment for Octamethylcyclotetrasiloxane (D4)* details the approach for estimating release days per year for Occupational Exposure Scenarios (OES). EPA used a Monte Carlo model to estimate daily release across sites (kg/site-day) and release frequencies across sites (days). The outputs of the model are a result of the model equations, equation input parameters and their associated distributions. For each OES a release pattern for the generic facility being modeled in terms of the kg/site-day of release and release days/site-yr are unknown. The days of release are calculated by dividing the annual release by the daily release. This is done due to factors such as the annual PV per OES being a constant value and/or constraints in the model such as a minimum and/or maximum daily throughput for a given process (*e.g.*, batch size constraints). This can cause the numerical value of the high-end (HE) release days (*i.e.*, the ratio of 95th percentile annual releases to the 95th percentile daily releases) to be smaller than the central tendency (CT) release days (*i.e.*, the ratio of the 50th percentile annual releases to the 50th percentile of daily releases). However, the HE number of release days corresponds to the HE daily and annual releases such that even though the HE number of release days is smaller numerically, it represents the more conservative release estimate (e.g., larger daily release but fewer release days). Please comment on the strengths and uncertainties associated with this modeling approach with specific emphasis on the role of greater release days for CT release distributions compared to days of release from HE release distributions.

Charge Question 5. Uncertainties Associated with Sediment Monitoring Data

Section 4.3.2.1 of the *Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4)* details the agency's interpretation of monitoring samples that are outside the calibration curve for sediment concentrations of D4. This pattern of very low surface water D4 concentration over elevated sediment D4 concentration is not apparent in other modeled or monitored OES. However, as noted in Section 2.2, D4 is not expected to be persistent in water but will be persistent in sediments. Please comment on EPAs interpretation of monitoring samples that are outside the calibration curve and the strengths and uncertainties of quantitative risk assessments that rely on these data.

Charge Question 6. Uncertainties related to releases to water

For eighteen COUs represented by thirteen OESs, the extent to which D4 may be released to water is unknown because available release information does not specify the media of release. In the absence of more specific release information, EPA currently has slight confidence in risk estimates related to releases to water for these OESs. In response to a related charge question on this topic in the phthalate peer review meeting, SACC reviewers advised EPA to assume that 100% of releases may go to water when specific information is not available in addition to recommending the use of a probabilistic approach for apportioning to media type. Appendix J of the *Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4)* presents a sensitivity analysis estimating what ecological risk quotients may result from different proportions of release to water for each of these OESs; however, in some cases D4 concentrations are well above solubility limits and well above concentrations detected in any monitoring data. For several OESs, risk quotients greater than 1 can result from surface water releases that are a small fraction (less than 1%) of the total released to all media. While this helps to define the conditions under which releases would result in ecological risks, EPA does not have sufficient information to determine whether these conditions actually occur. EPA is soliciting additional information on these releases that would help refine the analysis. Please comment on possible

approaches to refine this analysis to address the uncertainty while ensuring that resulting exposure and risk estimates are health protective, refined, and representative.

Charge Question 7. Bioaccumulation, bioconcentration, biomagnification, and potential trophic transfer

A survey of the bioaccumulation metrics for D4 are presented within the *Draft Physical Chemistry and Fate Assessment for Octamethylcyclotetrasiloxane (D4).* Media concentrations of D4 and potential sources of uncertainties are reviewed within both the *Draft Physical Chemistry and Fate Assessment for Octamethylcyclotetrasiloxane (D4)* and *Draft Environmental Media and General Population Exposure Assessment for Octamethylcyclotetrasiloxane (D4).* Section 3.6 of the *Draft Physical Chemistry and Fate Assessment for Octamethylcyclotetrasiloxane (D4)* details bioaccumulation potential of D4 while concentrations within aquatic species, terrestrial species, and biotransformation are reviewed within sections 3.1, 4.1, and 5 of the *Draft Environmental Exposure Assessment for Octamethylcyclotetrasiloxane (D4),* respectively.

7a. Detailed within the *Draft Physical Chemistry and Fate Assessment for Octamethylcyclotetrasiloxane (D4),* BAF is typically preferred when estimating human exposure to a chemical from fish ingestion because it considers the animal's uptake of the chemical from both the water column and from diet. However, there are considerable uncertainties associated with the field-measured BAF values available for D4 (*e.g.,* low detection frequency, unpaired fish/water field samples). EPA believes that the laboratory-measured BCF dataset is more robust. Moreover, D4 intake rates from dietary routes are low because D4 undergoes appreciable biotransformation in the gastrointestinal tract of fishes [for review see Section 5 of the *Draft Environmental Exposure Assessment for Octamethylcyclotetrasiloxane (D4)*]. Please comment on EPA's use of a BCF in lieu of BAF to estimate D4 concentrations in fish tissue and evaluate human exposure through fish ingestion, and the strengths and uncertainties of this approach.

7b. Section 3.6 of the *Draft Physical Chemistry and Fate Assessment for Octamethylcyclotetrasiloxane (D4)* details many sources of uncertainty in field- and laboratory-derived bioaccumulation metrics resulting from the study's design. Water samples for BCF and BAF studies should be analyzed to capture the bioavailable fraction. However, this can be difficult for D4 because of its volatility, hydrophobicity, and low water solubility. Furthermore, field studies introduce uncertainty when controls are not collected, sample sizes are small, steady-state conditions cannot be confirmed, and specific D4-contaminated food consumed by the fish is unknown. Although field measurements sometimes provide a more representative picture of accumulation dynamics in natural environments when compared to engineered laboratory settings, bioaccumulation metrics can also be skewed if low detection and quantification frequencies in the sampled biota are not taken into consideration. Because of the different uncertainties and strengths between laboratory and field studies, bioaccumulation metrics from both were considered in EPA's overall analysis of the bioaccumulation potential of D4.

i. Considering the inherent uncertainties associated with quantification of D4 in media and biota from field studies, as well as differences in the ability to control for exposure routes and concentrations between laboratory and field studies, please comment on the strengths and uncertainties of the selected data used for EPA's assessment of bioaccumulation metrics.
ii. Please comment on the strengths and uncertainties pertaining to EPA's preliminary conclusions surrounding biomagnification metrics.

7c. The *Draft Environmental Exposure Assessment for Octamethylcyclotetrasiloxane (D4)* provides trophic transfer analyses with modeled D4 concentrations from COU/OESs for different media of release and exposure pathways, and maximum values reported in the Enforceable Consent Agreement report (ECA) and peer reviewed literature for surface water, sediment, and soil. The screening level trophic transfer analysis was conducted by producing exposure estimates from the high-end exposure scenarios defined as those associated with the industrial and commercial releases from a condition of use (COU) and occupational exposure scenario (OES) that resulted in the highest environmental media concentrations.

i. Please comment on EPA's preliminary conclusions that D4 is likely to bioaccumulate in organisms but not magnify across trophic levels and therefore, trophic transfer analysis is not necessary for aquatic organisms.
ii. Please comment on the methods and data used for estimating dietary exposures for ecologically relevant species and discuss the appropriateness of the trophic transfer analysis for aquatic dependent mammals.

Charge Question 8. Fish Ingestion Exposure

Within the *Draft Environmental Media and General Population Exposure Assessment for Octamethylcyclotetrasiloxane (D4)*, D4 concentrations in fish tissue are calculated per specific COUs to estimate human exposure to D4 via fish consumption. Calculated D4 concentrations in fish tissue exceed U.S. monitoring data from the ECA by up to two orders of magnitude. In addition, the ECA's empirical fish tissue data are at least three orders of magnitude above measured concentrations across the available data landscape. As such, EPA believes that the maximum empirical fish tissue concentration from the ECA is an upper-bound of D4 concentrations in fish tissue. EPA therefore considered all calculated fish tissue concentrations that exceeded ECA's maximum empirical value as not representative of real-world scenarios. Please comment on the appropriateness of EPA's application of that upper-bound (i.e., ECA's maximum value) to define which fish tissue concentrations are realistic.

Charge Question 9. Identification of Hazards Relevant to Ecological Risk Assessment

Within the *Draft Environmental Hazard Assessment for Octamethylcyclotetrasiloxane (D4)* EPA assigned an overall quality determination of high to a single study with relevant toxicity data of D4 exposure to fresh water green algae (*Selenastrum capricornutum*). Springborn Laboratories (1990) show a 96-hour LOEC of 3.29 µg/L for the growth endpoint from a single concentration. There were minor testing discrepancies where algae were subjected to constant illumination and decreases in D4 concentration during open system testing that the authors attributed to volatilization. A closed system was used to limit volatilization of D4, and it was expected to have reduced growth rates due to lack of gas exchange. Growth of algae based on cell density at 96 hours exposure was significantly (Student's t-test) less than the control group. However, the LOEC derived from a single tested concentration was below the EC50 and the authors did not consider this level of reduction in cell density to be representative of an adverse effect. Therefore, an algae COC based on the LOEC concentration is expected to overestimate risk. The overall hazard confidence for aquatic plants (algae) was "slight" due to "robust" confidence for the quality of the database and "slight" confidence for: consistency, strength and precision, biological gradient/dose-response, and relevance. Please comment on the strengths and uncertainties of this algal hazard value, including relevance and confidence in the hazard database for this taxa.