OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

February 2, 2026

MEMORANDUM

SUBJECT: Transmittal of "Meeting Minutes and Final Report" for the Science Advisory Committee on Chemicals (SACC) Virtual Public Meeting for the Peer Review of the: "Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4), held on December 2-4, 2025.

FROM: Alaa Kamel, PhD
Chemist, Designated Federal Official
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TO: Elissa Reaves, PhD
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Office of Pollution Prevention and Toxics (OPPT)
Office of Chemical Safety and Pollution Prevention

Attached, please find the meeting minutes and final report for the Science Advisory Committee on Chemicals virtual public meeting held via Webcast on December 2-4, 2025. This report addresses a set of scientific issues being considered by the Environmental Protection Agency and reviewed by the SACC regarding EPA's Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4)

Attachment:
Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4)".

cc: Douglas Troutman
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Joel Wolf
Steven Dutton, PhD
Kesha Forrest, PhD
Anna Lowit, PhD
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OPPT docket
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Science Advisory Committee on Chemicals

Meeting Minutes and Final Report

No. 2025-3

Docket ID: EPA-HQ-OPPT-2025-1610

For the

Peer Review of the Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4)

Virtual Meeting via Webcast

Held on

December 2-4, 2025

NOTICE

The Science Advisory Committee on Chemicals (SACC) is a Federal Advisory Committee operating in accordance with the Federal Advisory Committee Act (FACA) and established under the provisions of the Toxic Substances Control Act (TSCA) as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act of 2016. The SACC provides advice, information, and recommendations to the US Environmental Protection Agency's (EPA or Agency) Administrator on chemicals and chemical-related issues regarding the impact of regulatory actions on health and the environment. The SACC serves as a primary scientific peer review mechanism of the EPA, Office of Pollution Prevention and Toxics, and is structured to provide balanced expert assessment of chemicals and chemical-related matters facing the Agency. Additional peer reviewers are considered and employed on an ad hoc basis to assist in reviews conducted by the SACC. The meeting minutes and final report are provided as part of the activities of the SACC.

The meeting minutes and final report represent the views and recommendations of the SACC and do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the Federal government. Mention of trade names or commercial products does not constitute an endorsement or recommendation for use. The meeting minutes and final report do not create or confer legal rights or impose any legally binding requirements on the Agency or any party.

The meeting minutes and final report of the December 2–4, 2025, SACC meeting represent the SACC's consideration and review of scientific issues associated with the Peer Review of the *Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4).* The SACC carefully considered all information provided and presented by the Agency, as well as information presented by the public.

The Science Advisory Committees branch of EPA's Office of Chemical Safety and Pollution Prevention/Office of Mission Critical Operations conducted the quality assurance and quality control of the meeting minutes and final report. The SACC Chair, Dr. George Cobb, and the SACC meeting Designated Federal Official (DFO), Dr. Alaa Kamel, compiled and certified the minutes and final report, which is publicly available through the e-docket No. EPA-HQ-OPPT-2025-1610 and is accessible through the docket portal at Regulations.gov and the "Peer Review of the Draf t Risk Evaluation for Octamethylcyclotetrasiloxane (D4)" web page of the SACC website. Further information about SACC reports and activities can be obtained from its website at TSCA Scientific Peer Review Committees. Interested persons are invited to contact the DFO for this meeting, Dr. Alaa Kamel, via e-mail at kamel.alaa@epa.gov, for questions regarding this peer review.

CONTENTS

CERTIFICATION

We, the undersigned, certify that the minutes in this report are an accurate and complete summary of the SACC's December 2–4, 2025, discussions of EPA's *Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4)* under the Toxic Substances Control Act (TSCA).

George Cobb, PhD
SACC Chair

Signature:

George P Cobb

Date: 02 February 2026

Alaa Kamel, PhD
Designated Federal Official

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ACRONYMS AND ABBREVIATIONS

ADME	Absorption, Distribution, Metabolism, and Excretion
AUC	Area Under the Curve
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
BMD	Benchmark Dose
BMDL	Benchmark Dose (lower confidence) Limit
BMF	Biomagnification Factor
BMR	Benchmark Response
BSAF	Biota-Sediment Accumulation Factor
CAR	Constitutive Androstane Receptor
CBI	Confidential Business Information
CDR	Chemical Data Reporting
ChemSTEER	Chemical Screening Tool for Exposures and Environmental Releases
COC	Contaminants of Concern
COU	Condition of Use
COVID-19	Coronavirus disease 2019
CYP	Cytochrome P450 enzyme
D4	Octamethylcyclotetrasiloxane
DA	Dopaminergic
DEVL	Dermal Exposure to Volatile Liquids model
DFO	Designated Federal Officer/Official
DMSD	Dimethylsilanediol
DOC	Dissolved Organic Carbon
ECA	Enforceable Consent Agreement
ER	Estrogen Receptor
GABA	Gamma-Aminobutyric Acid
GC	Gas Chromatography
GI	Gastrointestinal
GLP-1	Glucagon-Like Peptide-1 receptor agonists
GnRH	Gonadotropin Releasing Hormone
HEC	Human Equivalent Concentration
HED	Human Equivalent Dose
LH	Luteinizing Hormone
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOEL	Lowest Observed Effect Level
MLP	Mobile Lipid Pool
MOA	Mode of Action
MOE	Margin of Exposure
NOAEC	No Observed Adverse Effects Concentration

NOAEL	No Observed Adverse Effects Level
NOEC	No Observed Effect Concentration
OCSPP	Office of Chemical Safety and Pollution Prevention
OES	Occupational Exposure Scenario
ONU	Occupational Non-User
OSHA	Occupational Safety and Health Administration
PBPK	Physiologically Based Pharmacokinetic
PCBs	Polychlorinated Biphenyls
PCP	Personal Care Product
PESS	Potentially Exposed or Susceptible Subpopulation(s)
PF	Protection Factor
POD	Point of Departure
PPE	Personal Protective Equipment
PRL	Prolactin
PV	Production Volume
SACC	Science Advisory Committee on Chemicals
SEHSC	Silicones Environmental, Health, and Safety Center
TMF	Trophic Magnification Factor
TSCA	Toxic Substances Control Act
TSD	Technical Support Document
UCL	Upper Confidence Limit
UF	Uncertainty Factor
UF_A	Interspecies Uncertainty Factor
UF_H	Intraspecies Uncertainty Factor

SCIENCE ADVISORY COMMITTEE ON CHEMICALS

Review of the Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4)

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INTRODUCTION

The Science Advisory Committee on Chemicals (SACC or Committee), established pursuant to the Toxic Substances Control Act (TSCA) of 1976, as amended by The Frank R. Lautenberg Chemical Safety for the 21st Century Act in 2016, completed its review of the set of scientific issues being considered by the United States Environmental Protection Agency (US EPA, or Agency) regarding the review of the *Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4)*.

On September 10, 2025, EPA requested nominations of scientific and technical experts to be considered as ad hoc reviewers assisting the SACC with the peer review of the draft risk evaluation of D4 under TSCA (OCSPP Chemical Update-listserv). On September 19, 2025, a notice was published in the Federal Register (90 FR 45204), announcing the SACC meeting and requesting comments on the documents. The review was conducted in an open meeting held virtually via Zoom and streamed live on YouTube (see Meeting Viewing Information) from December 2-4, 2025. The *Draft Risk Evaluation for D4* and related documents supporting the SACC meeting are posted in the public e-docket at Regulations.gov, Docket No. EPA-HQ-OPPT-2025-1610. Dr. George Cobb chaired the meeting, and Dr. Alaa Kamel served as the Designated Federal Official (DFO) for this meeting.

The Committee carefully considered all information provided and presented by the Agency presenters, and information presented by public commenters in preparing these meeting minutes and final report. These meeting minutes and final report address the information provided and presented at the meeting, especially the Committee's response to the Agency's charge.

During the SACC meeting, the DFO, SACC Chair, and US EPA personnel provided the following presentations in the order listed below:

Opening of Meeting – Alaa Kamel, PhD, DFO Science Advisory Committees Branch (SACB), Office of Mission Critical Operations, Office of Chemical Safety and Pollution Prevention (OCSPP), EPA

Introduction and Identification of Committee Members – George Cobb, PhD, Chair, SACC

Introduction and Welcome – Joel Wolf, Acting Deputy Director for Programs, Office of Pollution Prevention and Toxics (OPPT), OCSPP, EPA.

Introduction to the Toxic Substance Control Act
Kesha Forrest, Chief, Existing Chemicals Risk Assessment Division (ECRAD), Office of Pollution Prevention and Toxics (OPPT), OCSPP, EPA

Part 1: Octamethylcyclotetrasiloxane (D4) Background
Chris Green, Susanna Wegner, ECRAD, OPPT, OCSPP

Part 2: Human Health hazard & D4 PBPK model
Edwin Arauz, Susanna Wegner, Celia Schacht, Miyoung Yoon, ECRAD, OPPT, OCSPP

Part 3: D4 Environmental Release Assessment
Joe Rappold, ECRAD, OPPT, OCSPP

Part 4: D4 Environmental Exposure Assessment
Jim Bressette, Chris Green ECRAD, OPPT, OCSPP

Part 5: D4 Bioaccumulation, Aquatic Biomagnification, and Trophic Transfer:

D4 Bioaccumulation
Andrea Amati, Jim Bressette, ECRAD, OPPT, OCSPP

D4 Aquatic Biomagnification
Andrea Amati, Jim Bressette, ECRAD, OPPT, OCSPP

D4 Trophic Transfer
Andrea Amati, Jim Bressette, ECRAD, OPPT, OCSPP

Part 6: D4 Fish Ingestion
Catherine Ngo, ECRAD, OPPT, OCSPP

Part 7: D4 Ecological Hazard
Jim Bressette, ECRAD, OPPT, OCSPP

PUBLIC COMMENTERS

Oral Presentations

Oral statements from the public were presented during the SACC meeting as follows:

#	Name	Organization	Location	Written version of presentation
1	Dimitri Abrahamson	University of California	San Francisco, California	EPA-HQ-OPPT-2025-1610-0072
2	Harvey Clewell	Ramboll	Monroe, Louisiana	EPA-HQ-OPPT-2025-1610-0073
3	Wolfgang Dekant	University of Wuerzburg	Wuerzburg, Germany	EPA-HQ-OPPT-2025-1610-0068
4	Robinan Gentry	Ramboll	Monroe, Louisiana	EPA-HQ-OPPT-2025-1610-0071
5	Frank Gobas	Simon Fraser University	British Columbia, Canada	EPA-HQ-OPPT-2025-1610-0069
6	Rashmi Joglekar (read by Dimitri Abrahamson)	University of California	San Francisco, California	EPA-HQ-OPPT-2025-1610-0074
7	Kathy Plotzke	Dow	Midland, Michigan	EPA-HQ-OPPT-2025-1610-0075

Written Comments

The following written comments were submitted in response to the peer review documents presented to the SACC:

#	Name	Organization	Location	Written version of presentation
1	Jon Arnot	NA	Toronto, Canada	EPA-HQ-OPPT-2025-1610-0051
2	Wolfgang Dekant	University of Wuerzburg	Wuerzburg, Germany	EPA-HQ-OPPT-2025-1610-0046
3	Vaibhav Gholap	NA	Pune, Maharashtra, India	EPA-HQ-OPPT-2025-1610-0041
4	Frank Gobas	Simon Fraser University	British Columbia, Canada	EPA-HQ-OPPT-2025-1610-0047
5	Tracy Guerrero	Dow Silicones Corporation	Midland, Michigan	EPA-HQ-OPPT-2025-1610-0050
6	NA	Ramboll Americas Engineering Solutions, Inc.	Syracuse, New York	EPA-HQ-OPPT-2025-1610-0049
7	Kent Woodburn	NA	Archer, Florida	EPA-HQ-OPPT-2025-1610-0048

NA=Not Available

EXECUTIVE SUMMARY

The Science Advisory Committee for Chemicals (SACC) commends the USEPA career scientists and engineers for preparing the *Draft Risk Evaluation for D4*, albeit without sufficient information or resources to conduct a comprehensive quantitative risk determination. The SACC notes its long-standing recommendations that describe basic data needs that have not been incorporated into current USEPA risk evaluations. Even at the screening level, risk assessments require data characterizing all substantial environmental releases across reasonably expected environmental media. Refinements would require additional details and use of appropriate mathematical tools to understand and appropriately aggregate the resulting information. EPA should be much further along than a screening-level assessment to make a risk determination, which would require no less data than needed for a screening-level assessment.

Additionally, full consumer exposure (including personal care products (PCPs) and food packaging, etc.), aggregate human health exposure, and complete ecological receptor assessments are required for a comprehensive risk evaluation. The current risk determination omits major portions, if not all, of these exposures. The USEPA has insufficiently considered age and other susceptible population differences. There is no evaluation of the potential for weight loss to influence exposure (given prevalent use of Glucagon-Like Peptide-1 receptor agonists (GLP-1 drugs) (see Díaz-González et al. 2024 as proof of concept). Furthermore, the measure chosen for assessing significant adverse physiological effects is focused on rodent litter size and survival. Although this is a responsive end point, it is one that is less sensitive than additional observed effects on the liver and other organs. The comparison of effect levels is difficult to discern in the absence of a diagram showing lowest observed effect concentrations (LOECs), no observed effect concentrations (NOECs), and the selected benchmark dose limits (BMDLs) for D4.

The SACC notes its previous advice that EPA requires the exposure scenarios mentioned above from manufacturers requesting risk evaluations to provide complete data packages that support reasonable exposure and effects assessments. This recommendation has not yet been addressed. The absence of adequate information to formulate a health protective risk determination continues to be an issue. “Adequate information” includes harvesting contemporary, reliable, and relevant information from industry, the marketplace, transportation, and occupational organizations (such as unions, academia, industry research), as well as federal, state, and community agencies. Standards of reliability regarding the information can be based on proven practical knowledge; marketplace standards; professional standing; publication in relevant and professionally recognized venues, including but not restricted to peer-reviewed manuscripts; community acknowledgment; or review by agency (state, regional, national, international) authorities. Topics should establish health hazard metrics and all sources and conditions contributing to exposure routes for all subpopulation groups.

The *Draft Risk Evaluation for D4* has an assessment of D4 release to water but has no assessment of releases to air, and data describing D4 transformation in soil are inadequate to provide a reasonable evaluation of D4 behavior in soils. Moreover, the *Draft Risk Evaluation for D4* contains virtually no data that were collected by EPA or the manufacturers requesting the evaluation in the last seven years. Thus, the current risk determination is more of a screening-level assessment with inclusion of some mathematical manipulations that do not in essence refine the D4 risk assessment in a verifiable way.

The SACC has previously recommended that risk evaluations should not consider the use of personal protective equipment (PPE) when evaluating risks to workers. PPE and other control measures do play an important role in risk management, and that is where they should stay.

This SACC report begins with a discussion of omissions noted in the preceding paragraphs and moves to the limited questions that the EPA management allowed as part of the charge. The USEPA inquired about the suitability of the Physiologically Based Pharmacokinetic (PBPK) model. There were also charge questions about appropriate toxicity endpoints and inhalation studies for human health assessment. The Committee also answered charge questions related to estimating production volume and release days in the absence of data that are needed to include those parameters in the D4 release estimation. Topics of uncertainty in D4 sediment monitoring and release to water were identified. The charge questions of D4 bioaccumulation and biomagnification were addressed along with an evaluation of fish consumption by humans. Finally, the toxicity of D4 to algae was evaluated.

The Committee commented extensively regarding the inadequacy of production and manufacturing data—significant omissions which adversely impact the understanding of exposure opportunities for workers, bystanders, consumers, and the general population. The absences of environmental releases to air were noted as significant omissions in the environmental release data, which is an important consideration given the noted volatility of D4 and the significance of fugitive emissions during D4 manufacturing, distribution, and use.

More specifically, and as illustrated by the preceding paragraph, the issue of adequate information continues to be ill defined and raises questions. Information within EPA's TSCA risk assessments should establish health hazard metrics as well as all sources and conditions contributing to exposure opportunities for all subpopulation groups.

Use of the D4 PBPK Model

Evaluation of the PBPK performance was hampered by inadequate review time for the SACC to evaluate the model algorithms, functional integrity, and imbedded assumptions. As the information for the review proceeded, there was insufficient time for SACC members to obtain and access the model for substantive evaluation. These time limitations could have been mitigated by earlier dialogue with the SACC about the charge and by the addition of ad hoc members with significant PBPK model expertise to the SACC for this D4 review. The SACC noted the PBPK model worked adequately on the uptake phase and suggested some ways the model could be improved to allow better performance in the clearance phase and in the dynamic range for the uptake phase. As noted above, the model cannot consider metabolic consequences of toxicant "dumping" during rapid fat loss—a phenomenon of growing relevance in human populations and could be a significant source of acute "re-exposure." EPA should also consider modeling D4 absorption, distribution, metabolism, and excretion (ADME) more broadly in obese individuals, since this concerns a significant portion of the American population (35–40 percent). Thus, it is not only the GLP-1 drug mediated weight loss that pose a concern; depot effects in obese individuals are also a concern.

The Committee appreciated the general content of the model description and review provided by the Agency, in particular the historical overview in Section 1.5 (US EPA 2025i). However, various clarifications are recommended.

The expertise of the ICF contractors providing the assessment of the Campbell (2023) model needs to be expressed in the document to provide transparency and confidence.

There are strengths to this PBPK model for outputs related to internal dosimetry, animal-to-human extrapolation, route-to-route extrapolation, duration extrapolation, and the point of departure (POD) derivation, but uncertainties exist and should be addressed. The Committee assessed that the central source of uncertainty is the model's strong reliance on fitted parameters, particularly partition coefficients as mentioned in the response to charge question 1a, that were optimized to match specific rat inhalation datasets rather than derived directly from measured physicochemical properties.

Regarding dermal exposure and risk, while the Committee agreed with EPA's conclusion that the levels of absorption generally observed by the dermal route for D4 appear to be relatively low based on both the PBPK model output and the limited available empirical human health *in vivo* data, the discussion by EPA of the potential sources of uncertainty regarding use of this approach should be expanded and clarified. EPA should also consider using more relevant values for quantitative skin loading (Q) in its dermal exposure assessment. The current values being applied are not specific to volatile liquids. And EPA should provide additional rationale and support for the assumptions around the occluded dermal exposure scenarios applied in the risk evaluation, as these assumptions are not adequately supported in the current draft risk evaluation.

The Committee supported the general use of PBPK modeling and concepts and also applauded the Agency's recognition of uncertainty that the application of the PBPK model, which was designed for adults, could be used to reliably assess D4 risk to children. Extrapolation from adults to children is a significant uncertainty for the PBPK modeling approach. The Committee commented on multiple aspects unique to the reliability of the model itself for assessing children as well as the applicability of the model to conditions of use (COUs) and attributes specific to the COUs within the risk evaluation. Importantly, the Committee noted that the scope of the charge question is large and complex. The Committee could not conduct independent research or run the model independently to robustly address this complex issue, including model performance for various ages or reproductive status. Therefore, the SACC made two specific recommendations to the Agency for conduct of additional research and development of a more technical rationale on this important aspect of the risk evaluation.

Human Health Hazard Assessment

A large body of literature links adverse effects of D4 exposure (generally via inhalation) to adverse reproductive outcomes, particularly in females; males do not show the same extent of adverse effects. These effects center around female reproduction, including estrous cycle disruption as well as a reduced number of implantations and live births. The various studies used test subjects from a range of ages, which is important for understanding life stage differences detected in the adverse effects of D4 exposure. There were studies in both in humans and rodents.

There was general agreement that selection of hazard endpoints and studies to support POD derivation was supported by the Agency's thorough review of the evidence developed from the systematic review process, although an updated literature search and improvements to document discussions and data presentations were recommended. A more complete mode of action (MOA) analysis is warranted for both the reproductive and liver effects, considering updated literature, Committee comments, and public input.

The most important process for forming D4 in the workplace is through condensation of vapor. The conditions that favor aerosol formation include temperature, the presence of airborne nuclei, (tiny particles around which a vapor can condense) and other factors. Understanding these conditions is crucial for assessing exposure risks. The difficulty in measuring both vapor and aerosol concentrations simultaneously complicates exposure assessments. Current EPA data primarily focus on vapor exposure, which may not fully capture the potential risks associated with aerosol exposure.

The reliance on inhalation studies using vapor exposure raises questions about the potential pulmonary toxicity of aerosols. The particle size of aerosols is critical for understanding potential sites of deposition in the respiratory tract and their associated health effects. The distinction between aerosol and vapor exposure is important for risk assessment. The potential for aerosols to be generated in various conditions, including high concentrations and specific applications (like spraying paints), necessitates a thorough evaluation of both exposure routes. The lack of epidemiological studies and specific data on aerosol particle size distribution contributes to uncertainties in assessing the health risks associated with D4 exposure.

Use of benchmark dose (BMD) guidance and model selection for dose response analysis was generally supported. While no particularly substantive suggestions are offered from the SACC on the specific application of the BMD software, the SACC offered a number of comments related to study, endpoint, and model selection. Because BMDLs at 5 percent are sensitive to variation in response, and because there were questions about study and endpoint selection, it is recommended that the EPA provide a scatter diagram of no observed adverse effects level (NOAELs) and lowest observed adverse effects level (LOAELs) for specific endpoints relative to the POD to aid in interpretation.

As discussed above, reproductive endpoints served as the primary basis for quantitative dose-response analysis, and included mean litter size, mean number of pups born, and fertility from the evidence in a two-generation inhalation study. These measures were reliable at exposure level of 700 ppm. There were also more broad responses to this charge question that relate to dose-response step in the evaluation, specifically that additional responsive end points were detected in this and other studies that could provide a more sensitive and reliable index of D4 toxicity.

Additional details and/or documentation for the modeling are needed, including rationale for study, endpoint, and model selection, as well as rationale for possible deviations from standard guidance. It is recognized that EPA has undertaken a substantial effort through the systematic review, and the SACC recommends that the EPA take additional measures to report how information from the review was used in context of the decision to select a single study rather than modeling several studies to inform POD

selection, thus ensuring that the PODs used in the risk evaluation are both representative of the body of evidence and are sufficiently protective.

Use of Chemical Data Reporting Production Volume for the Environmental Release Assessment

Production volumes of D4 are inadequately documented. Claims of Confidential Business Information (CBI) obscure the situation and are unacceptable for a manufacturer requested review. The EPA and the SACC are capable of managing and evaluating such data appropriately. The SACC questions the EPA's selection of CBI obscured production data from the Coronavirus disease 2019 (COVID-19) pandemic era. Such selection must be well justified. More appropriately, EPA should obtain needed production and manufacturing information.

Number of Release Days for Modeled Environmental Releases

Data underlying the analysis of release days are poor. More complete and appropriate industry data are urgently needed. In the meantime, EPA should treat upper-bound production volume (PV) values as justified defaults (given lack of industry data to prove otherwise) and highlight the large drop in PV reporting from previous years and the uncertainty introduced by the unexplained production drop. EPA could carefully consider two or three common facilities to determine the probability that they would exceed high exposure load on any given day. Evaluating these facilities in depth could help to confirm some of the assumptions made by EPA. EPA should also extend Monte Carlo modeling to evaluate cumulative emissions from multiple nearby sources and rely on distributions showing high frequencies of release days when assessing realistic daily load contributions.

Uncertainties Associated with Sediment Monitoring Data

The Committee supported the use of sediment monitoring data and recommended clearer documentation of calibration exceedances, more consistent definitions of analytical limits, and improved transparency in uncertainty communication to achieve scientific rigor and clarity of the sediment data interpretation within the overall risk evaluation for D4. In this case it should be noted that quantifiable D4 in sediment often exceeds the calibration range, and, as such, these sediment data should be considered as low estimates of the actual D4 in those samples.

Uncertainties Related to Releases to Water

The Committee agreed that the current assessment appropriately acknowledges uncertainty regarding the extent of D4 releases to water for 13 occupational exposure scenarios (OESs) representing 18 COUs. Additional accurate information is needed not only to describe releases to surface water, but also to identify those releases subject to wastewater treatment that is highly effective at removing D4 in effluent. It is important to know the D4 releases attributable to wastewater treatment or to other point sources. In the absence of accurate release information, modeled "releases to water" in the *Draft Risk Evaluation for D4* may overstate realistic exposure, since the empirical monitoring indicates low D4 concentrations in surface water despite measurable sediment residues. Committee members noted that in the absence of additional release information, the current assessment would benefit from additional refinement to ensure that modeled assumptions are both health-protective and representative of real-world conditions.

Bioaccumulation, Bioconcentration, Biomagnification, and Potential Trophic Transfer

The use of the bioconcentration factor (BCF) instead of the bioaccumulation factor (BAF) is supported by the evidence in the *Draft Environmental Exposure Assessment for Octamethylcyclotetrasiloxane (D4)*. However, the Committee expressed some concerns about the parameters considered when using selected specific data to rationalize the use of BCF, including consideration of the lipophilic nature of D4, potential for exposure in aquatic organisms, use of laboratory versus field produced evidence, and translating laboratory findings to risk estimation. In theory, BAF should never be lower than BCF because BAF integrates dietary exposure as well as gill exposure, but BCF does not. Rather than substituting BCF for BAF, EPA should adopt mechanistic, scenario-based bioaccumulation modeling, using models such as the ADME-B model already adopted in the report, with (1) calibration to reliable lab kinetics (the same datasets supporting the "high-confidence" BCF values identified by the EPA); and (2) explicit considerations of different scenarios characterized by those highly variable inputs (like diet). This should be possible, given that the EPA has already used the ADME-B model to determine BCF values under different scenarios of dissolved organic carbon (DOC) content. Using mechanistic, scenario-based bioaccumulation modeling will help avoid "apples to oranges" mixing of field and lab metrics and prevent a precedent where a BCF is used simply because it is larger (and seemingly "protective") than an uncertain BAF.

In the D4 case, although using the maximum BCF values happens to be more protective than using BAF values, presenting this in the report may be problematic as it may be misinterpreted as setting a methodological precedent for doing such replacement in future chemical assessments. If used in this way, there is the potential of promoting the misuse of BCFs.

It is essential for the EPA to assess the uncertainties associated with field measurements. The exclusion of data from well-designed field studies is not recommended, and any reasoning for doing so must be clearly articulated. Studies with BCF and BAF ranges shown in the *Draft Physical Chemistry and Fate Assessment for Octamethylcyclotetrasiloxane (D4)* (US EPA 2025g, 43, Figure 3-5) provide a more direct comparison of bioconcentration and bioaccumulation data in fish, illustrating large variation potentially due to multiple factors influencing uptake. Given the uncertainties and the limited trophic range of the field measurements, a BCF based on those data would have uncertainties. More data or a more detailed uncertainty analysis is required to appropriately address this issue.

The SACC appreciated the extensive review of available literature that is pertinent to biomagnification. The preliminary conclusion about uncertainties related to biomagnification metrics has merit, especially given the variability of information from field studies. It is not entirely clear that the field studies included in this risk evaluation should be considered when determining biomagnification. It is perhaps preferable to use laboratory studies as foundational information with more controlled conditions. In addition, the public comments submitted by Dr. Frank Gobas highlighted uncertainties associated with the less reliable low-quality data points; e.g., small trophic span, inadequate sample sizes, and incorrect use of lipid normalized biomagnification factor (BMF) equilibrium constant (k values), whereby it is quite important to select only high-quality data for further improvement of the biomagnification assessment. Additional analytical approaches are suggested for consideration by the EPA.

Fish Ingestion Exposure

The SACC found that EPA's approach to estimating fish tissue concentrations of D4 for use in ecological and human health screening assessments is likely to substantially overestimate environmentally realistic exposure for an average person. The Committee noted that modeled fish tissue concentrations were derived from highly conservative surface water concentrations multiplied by laboratory-based BCFs, and the overestimation would result from compounded conservatism, including assumptions of low organic carbon, constant BCFs across exposure ranges, and inadequate data sets to refine worst-case discharge scenarios. Each of these refinements would contribute to reduced bioavailability of D4 in natural waters.

Given these limitations, the Committee agreed with EPA's decision to use the maximum empirically measured fish tissue concentrations from the Enforceable Consent Agreement (ECA), (ERM, 2017) as an upper bound for screening purposes. Although the ECA dataset has notable shortcomings, including limited spatial and temporal representativeness, uncertainty in fish residency within wastewater plumes, and data quality flags on the maximum observed concentration—it provides the most defensible basis among the available data for identifying a plausible high-end exposure estimate.

The Committee emphasized, however, that the maximum observed fish tissue concentration should be characterized as a *plausible upper-bound screening value*, not as a realistic or representative exposure for the general population or specific subpopulations. Clear distinction between screening-level high-end values and representative exposure estimates is essential for transparent risk communication.

Finally, the Committee identified significant gaps in the exposure assessment for Tribal populations. By focusing solely on fish consumption and omitting other relevant exposure pathways—such as drinking water ingestion, dermal contact, and consumption of other subsistence foods, the current assessment likely underestimates exposure and does not reflect real-world conditions experienced by Tribal communities.

Identification of Hazards Relevant to Ecological Risk Assessment

The SACC concurred with EPA's determination that the Springborn Laboratories (1990) study using the green alga *Selenastrum capricornutum* is not appropriate for use in the ecological hazard assessment. Although the test species is environmentally relevant and the study followed a standard protocol with acceptable quality assurance and quality control, the experimental conditions substantially limit the relevance of the results to natural environments. In particular, the use of a closed system with no headspace, restricted oxygen exchange, and test concentrations at the functional solubility limit introduces confounding factors that are unlikely to occur under environmentally realistic conditions and consequently may overestimate toxicity.

The Committee also provided comments on EPA's assessment of risks to sediment-dwelling organisms. Key concerns included uncertainties associated with sediment concentration measurements that exceed calibration limits, communication of confidence and uncertainty in risk conclusions, and apparent inconsistencies in reported acute and chronic toxicity thresholds. Collectively, these issues affect interpretation of ecological risk assessment and warrant clarification with improved transparency in the supporting documentation.

DETAILED COMMITTEE DISCUSSIONS AND RECOMMENDATIONS

Important Issues Raised by the Committee but Not Addressed by EPA's Selected Charge Questions

Omission of likely sources of exposure

In preparation for this D4 review, the SACC requested that EPA add a charge question regarding the completeness of the inhalation exposure assessment. In response, EPA stated: *"*[i]ndoor air concentrations from personal care products (PCPs) were not considered quantitatively in part because they are outside of EPA's jurisdiction.*"* Ultimately, the charge question was not included in the final charge to the Committee*.* The SACC has repeatedly advised EPA that a scientifically credible risk assessment must include *all* reasonably expected and substantial exposures. Probabilistic aggregate exposure assessment considering all potential D4 sources should be conducted with expression of the relative contribution to overall exposure from each source. The proportional exposure contribution from sources under authority of TSCA can then be understood when considering further assessment needs and/or risk mitigation strategies. Additionally, in the *Draft Consumer and Indoor Dust Exposure Assessment for Octamethylcyclotetrasiloxane (D4),* EPA included risk evaluations from consumer products indoors, focusing on D4 exposures from COUs less likely to cause human exposures (US EPA 2025b, 27–28). Thus, there is no scientifically credible rationale for excluding PCPs from the *Draft Risk Evaluation for D4* (US EPA 2025h). The SACC recognizes that the EPA may not be able to regulate the use of D4 in cosmetics, food packaging and medical uses, but these exposures are also needed for the D4 risk determination. Only after exposures from PCPs, cosmetics, food packaging, and medical uses are incorporated into the risk determination can an informed risk management decision can be made. If, as EPA has asserted, other agencies have assessed the safety of the products currently excluded from the D4 Risk determination, then exposure values from those assessments can be included to better understand D4 exposures for manufacturers, suppliers, users, and bystanders, as components of an aggregate human exposure assessment for each potentially exposed group. Interestingly, the Dermal Absorption portion of the *Draft Risk Evaluation for D4* contains simulated uptake from anti-perspirant application, but this is not a part of the consumer assessment. For exposure routes without D4 exposure values from the regulating agency, exposure from that route use must be assessed by EPA. To do otherwise leaves the public and the broader environment unprotected and renders the 2016 Lautenberg Chemical Safety for the 21st Century Act (Public Law, 2016) largely meaningless. If EPA chooses not to assess these risks from such exposures, very specific language must be provided to indicate the extent to which other US agencies have performed relevant risk determinations that address exposure and effect issues detailed in the Lautenberg Chemical Safety for the 21st Century Act. This language must define how these other agency risk assessments have addressed COUs that EPA considers outside of their regulatory authority. The Committee has identified no evidence that worker, user, bystander, or non-user exposures to these excluded COUs have ever been evaluated by a US regulatory authority. The EPA must explicitly list all COUs that EPA has chosen not to assess due to another agency having regulatory authority. Unassessed COUs (i.e., cosmetics, cooking, and PCPs) leave humans and ecological receptors at unknown and potentially high risk from D4 exposures.

EPA has improperly excluded D4 content in commercial products (see US EPA 2025b, 12). Also, in the *Draft Risk Evaluation for D4,* EPA refers to a *Draft Consumer and Indoor Exposure Assessment for Octamethylcyclotetrasiloxane (D4)* (US EPA 2025h, 138). But that document has been replaced with *The Draft Consumer and Indoor Dust Exposure Assessment for Octamethylcyclotetrasiloxane (D4).* Given the Agency's heavy reliance on the volatility of D4 to justify calculations of low concentrations in soil, it is not reasonable to limit indoor exposure to dust. If D4 volatilizes from soil, it will also volatilize from dust. EPA must explain what happened to the original "Indoor Exposure Assessment." Did it contain evaluations of vapors and aerosols in addition to dust? EPA must also include human (adults and children) exposure to indoor D4 vapors and consider differing sensitivity to exposure over the lifespan.

EPA's failure to include consumer use of D4 in PCPs (US EPA 2025h, Table 5-6) directly limits estimates of D4 discharges to water in the DRE. Furthermore, it is difficult to discern the extent to which EPA excluded or chose not to evaluate use and exposure information. In the *Draft Environmental Media and General Population Exposure for Octamethylcyclotetrasiloxane (D4),* (US EPA 2025d), aqueous exposures are modeled through the Point Source Calculator using water releases; tracking those releases to the *Draft Environmental Release and Occupational Exposure Assessment for Octamethylcyclotetrasiloxane (D4)* leads to information that does not include direct releases (volatilization and dissolution from skin or commercial products into surface waters) from consumer products. Thus, the circular references in the assemblage of documents in this docket do not contain a comprehensive assessment of general population exposure to D4 sources other than direct industrial releases from manufacturing or from water treatment plants. This is a significant omission and must be corrected.

In the *Draft Environmental Media and General Population Exposure for D4,* EPA should clearly state whether the assumed ambient air exposures in Table 9-1 are mean values or high-end values (2025d, 65). Further clarification is needed regarding whether EPA excluded D4 releases during manufacturing and formulation of personal care, medical, and food handling products in this assessment. The summary on page 8 of the *Draft Environmental Media and General Population Exposure for D4* includes a statement comparing modeled D4 concentrations in soil and in air to monitored concentrations; however, it is unclear what the monitored concentrations are. EPA must state what monitored air and soil concentrations of D4 were used in the *Draft Risk Evaluation for D4* and briefly describe them.

The Table on page 9 of the *Draft Environmental Media and General Population Exposure for D4* includes a statement comparing modeled D4 concentrations in soil and in air to monitored concentrations. It is unclear what the monitored concentrations are. These monitored data must be described and summarized in the D4 the *Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4).* On LL 287, the EPA claims to have used available information about releases, but the *Draft Environmental Release and Occupational Exposure Assessment for D4* does not contain any monitored data that describe releases to air from manufacturing facilities. If there are no actual release data, that must be stated. Further, the statement on page 9 of the *Draft Environmental Media and General Population Exposure for D4* regarding environmental monitoring data within the ECA could be misconstrued to indicate that D4 concentrations in air and soils were evaluated in the ECA work, but they were not. This statement must be rephrased to indicate that the report included monitoring of water, sediment, and select aquatic biota.

The EPA should not omit milk ingestion by infants from this evaluation. Available information shows that this is a possible exposure route. However, the risk for children is based on adult estimates. The long-term effects from early exposure should be considered. In part because it is a relatively simple thing to evaluate from the available data (Kaj et al. 2005). The reported upper range of D4 concentrations in human milk is 2.9-10 ug/L, which represents three quantified values of 39 samples. Using these data and a Human Equivalent Dose for 30-day D4 ingestion of 3.6 mg/kg-bw/d, the hazards that D4 poses to a 3 kg newborn infant can be calculated. In this worst-case scenario, a human equivalent dose (HED) would be reached at 1080 L of milk/day (3.6 mg/kg-bw/d *3 kg/0.01 mg/L). A 10X uncertainty factor (UF) for concentration uncertainty and another 10X for response of a sensitive life stage would leave 10.8 as the margin of exposure (MOE) for an infant consuming 1 L of human milk per day. Of course, this evaluation does not include other types of milk (e.g., bovine) normally consumed by children.

There does not appear to be any toxicological evaluation of D4 transformation products in humans or environmental receptors. This must at least be qualitatively addressed.

Significant exposure opportunities have been omitted, and these exposures are relevant to general public, potentially exposed or susceptible subpopulations (PESS) and non-occupational population groups. Wholly absent or under-represented exposure scenarios include:

- Exposures to complex products, including transportation vehicles: busses, metro, planes, etc. Issue: repeated exposures in closed container vehicles for long periods of time on those days when used. Exposures often on a daily basis to all age groups.
- Overall exposures to all age groups from containers or utensils used in the home for storage, wrapping, (food, of course, but also a myriad of other uses for containers, plastic wraps, coverings for clothing), liners, shoes, heat resistance, etc.
- Occupational exposures to workers and exposures to residences near large distribution centers from building exhaust.

The work in the BMF portion of the *Draft Physical Chemistry and Fate Assessment for D4* is good but could be improved. EPI Suite™ Modeling can be improved to better estimate D4 fractions and half lives in compartments. EPA has modeled D4 releases to air and has measured or modeled D4 releases to soil. An added factor of releases to air from consumer products can be obtained from studies in Chicago (Yucuis et al. 2013) and New York City (Brunet et al. 2024). These values should be added to the airborne release amount. With these data or estimates, discharges to each compartment can be expressed as mass per time and entered directly into the EPI Suite™ to better estimate D4 releases and thus improve the model estimate of D4 behavior in the environment.

Personal Protective Equipment Use

The SACC has repeatedly advised EPA that risk evaluations should not consider the use of PPE in evaluating risks to workers. PPE and other control measures do play an important role in risk management, and that is where they should stay. PPE use did alter findings of unreasonable risk, and the fact that EPA estimated PPE impact on worker exposure signals that EPA considers PPE to be a primary, if not the only, means of control applicable into the workplace. EPA's position is entirely inconsistent with

the well-established processes for risk management that list PPE (both respirators and gloves) as the least desirable control for worker exposure reduction.

However, if EPA wishes to venture into risk management at this stage, it should at least recognize that many other measures should be considered first; these include elimination, substitution, engineering controls, and modifications of work practices, in that order. This is known as the hierarchy of controls (NIOSH 2024, OSHA 2023). PPE comes last in the hierarchy. Every other agency that regulates or studies workplace controls considers PPE to be the last resort. These include the Occupational Safety and Health Administration, Mine Safety and Health Administration, Department of Energy, and National Institute for Occupational Safety and Health. Please note that three of these agencies are directly responsible for worker health. So, controlling exposures through other means must be considered before PPE is considered, and all of that is a risk management decision, not a risk assessment decision. The *Draft Risk Evaluation for D4* gets this right in Section 5.3.2.1, but the document goes on to consider only PPE as a control measure in other sections. For example, in the executive summary, the draft states:

> …the Agency preliminarily identified a total of 24 COUs where occupational exposure for workers, including occupational non-users (ONUs), without personal protective equipment (PPE) significantly contributes to unreasonable risk of injury to human health… When applied, the use of PPE is found to mitigate the unreasonable risk to workers. (US EPA 2025h, 14)

It would be better to say:

> …the Agency preliminarily identified a total of 24 COUs where occupational exposure for workers, including ONUs, can cause an unreasonable risk of injury to human health… When applied, the use of effective industrial hygiene measures, following the hierarchy of controls, would mitigate the unreasonable risk to workers.

It would be better yet to eliminate any discussion of PPE in this and other sections, especially the columns comparing presumed exposures with and without PPE, summaries in Section 5, and the discussion of unreasonable risk in Section 6.2.4. However, other types of more reliable and consistent controls (such as isolation or ventilation) can and do have an effect on exposures that is directly measurable and would be far more appropriate to consider in the determination of risk.

In the case of respirators, even when an employer follows OSHA's Respiratory Protection Standard, some workers may not achieve a 10-fold reduction in exposure. Many people are familiar with the N95s and KN95s used during the pandemic. Those respirators are useless against chemical vapors; they are nothing like the elastomeric masks strapped tightly to the face for protection against chemical exposures. A tight-fitting mask is very difficult to wear for a full shift, and many workers often pull them away from their faces to get a little relief. It is very difficult to communicate through a respirator, so workers must pull them away from their faces to be heard. Chemical plants can be hot, and sweat can interfere with the respirator seal. Organic vapor cartridges can become saturated and must be regularly replaced. At times, they are not. The assigned protection factors on which EPA relies do not take these issues into account. They are based on the fit to a normal face under good conditions, and the effectiveness of the filter.

Some workers cannot wear respirators at all. Workers with unusually shaped faces or facial scars may not get a good fit from air-purifying respirators. (Some of these workers can wear powered respirators, but they require belt-mounted batteries, and filter cartridges and are expensive.) Respirators create breathing resistance, so workers with respiratory problems or heart disease may not be able to wear them. They can be risky for older workers, and doctors administering the annual exams required by OSHA may not certify an older worker to wear one.

Unlike other controls, respirators do nothing to lessen the concentration of chemicals in workplace air. This consideration is especially important when evaluating exposure of workers and ONUs, to D4 in the workplace, and of broader population exposure to fugitive emissions in the ambient air near a facility handling D4. If airborne D4 within facilities is allowed to remain high because workers are assumed to be protected by respirators, then the fugitive emissions from air exchanges for these facilities will by definition be higher, unless additional air pollution control measure are taken. For D4, the problem is amplified by the fact that (1) There are no outdoor atmospheric monitoring data for D4 at any facility, even though this is a manufacturer requested review; and (2) The largest percentage of D4 estimated to be released into air from manufacturing and packaging operations is from fugitive emissions.

Physical Chemical Parameters and Soil Dissipation Studies

In the *Draft Physical Chemistry and Fate Assessment for D4*, a 1997 Dow Corning document (also noted as Springborn Labs 1991a) is cited as the sole study related to D4 degradation in soil (US EPA 2025g, 30). Earlier in the same document, peer-reviewed studies of D4 dissipation in soil are detailed and should be mentioned. It also seems two of the peer-reviewed studies regarding D4 removal from soil simply reanalyze the same underlying Dow data. The Committee has several concerns with the underlying study by Xu and Chandra (1999). No D4 or transformation product masses are reported at any point in the article and 2) the analytical methods report insufficient method performance data, 3) the interpretation of no microbial degradation is not supported by any sterilized soil experiments, and 4) the selection of soils is questionable.

Without D4 and transformation masses, it is impossible to determine if the mass balance is based on the amount of D4 introduced into the test systems (30ml vials containing soils) or the amount of D4 retained by soils after purging the vial's headspace with air. This is an essential consideration since vapor purging was only used for the sealed test systems for "degradation" but not for unsealed test for overall D4 dissipation. The amount of D4 added to each container (217ug or 0.073 umole) was less than the amount of D4 that each vessel's headspace could contain at D4 saturation at 25C (1 mm Hg). Thus, volatilization during the purge phases of the sealed container test may have removed significant portions of D4 from the test system and left smaller amounts of D4 to be degraded in the soil. It is important to note that the open tube experiments were not purged with air. Thus, there was no comparison of D4 masses obtained at time zero for opened and sealed containers.

For the Michigan soils, dissipation rates ($t_{1/2}$ of = 5.25d) could well have been effected by purge times, extraction times and possible acclimated microbial communities in the soil. It is also possible these acclimation concerns exist for selected Hawaiian soils, depending on whether those soils were part of, or near, the Dow research facility there. The Hawaii soils are weathered volcanic materials with anomalous

chemical catalytic properties that enhance degradation over normal soils. These soil attributes raise the question: Why were the only two soils tested: 1) a Michigan soil where D4 is produced and 2) a Hawaii soil type that is rare outside that region of the US and perhaps on a D4 exposed research site? These concerns increase when considering: 1) the lack of a verifiable mass balance and 2) time zero D4 amounts that are either missing or residing in the range of 60% D4 remaining. Thus, in the absence of a verifiable mass balance, the soil dissipation study that EPA selected for D4 degradation in soil is at best a dissipation study with uncertainties.

Those studies did not meaningfully investigate, measure, or test the biodegradation (microorganism-mediated chemical transformation) pathway. Although they acknowledged biodegradation conceptually, they concluded that D4 degradation is predominantly abiotic and, as a result, did not measure or test microbial degradation as a contributing process. As the authors said, "In addition, no significant amount of $14CO_2$ evolved from 14C-labeled D4 in a water/sediment system with active microflora, implying that cVMS cannot be mineralized directly by microorganisms." (Xu and Chandra, 1999). In fact, this reasoning is logically flawed. While all mineralization is a form of biodegradation, not all biodegradation necessarily results in mineralization. The absence of CO_2 evolution does not rule out microbial transformation. In fact, there are many well-documented cases (e.g., with DDT) where microbes biodegrade a compound without fully mineralizing it. Because t1/2 is determined solely by the disappearance of the parent compound, not explicitly accounting for the impact of biodegradation could be problematic.

Additionally, the soil with the slower D4 dissipation rate was obtained from the Michigan county where Dow silicones operations are located. Microbial acclimation is a significant concern for these Michigan soils. These acclimation concerns may exist for the selected Hawaiian soil type, depending on whether the Hawaii soils were part of, or near, the Dow research facility there. These facts, raise the question: Why the only two soils tested originated from areas of Michigan where D4 is produced and from a soil type in Hawaii that is rare in other areas of the US and that may have been part of a DOW research station. Perhaps both soils were from locales where microbes were acclimatized to D4 exposure? The lack of a verifiable mass balance in these studies increases these concerns.

D4 volatilization from landfills is tabulated in this draft risk evaluation (DRE). This documented volatilization provides evidence that D4 is unlikely to have degradation half-lives that are used by EPA in this DRE. If the D4 half live is 0.04-5 days, as reported (Chandra et al, 1999), landfills should not be emanating significant amounts of D4 to the surrounding air. If the Xu and Chandra (1999) study is used to explain D4 fate in the environmental, it should be used to describe D4 dissipation from soil dissipation, and the term dissipation should be used rather than degradation or hydrolysis. Addressing these concerns will also require further and more robust assessment of inhalation risks from D4 that emanates from soils and sludges (*i.e.* industrial solids and wastewater).

No method performance data are provided for the extraction methods with the tested soils. The limited ability of hexane to "wet" moist clay surfaces would likely insulate the D4 on the surface and allow D4 to remain there until the next extraction step. The committee also questioned the ability of the aqueous calcium chloride to fully access any transformation products from the hexane inundated soils. Also, the graphs show what appears to be D4 residual fraction at time zero in the Wahiawa Hawaiian soil type at

32% relative humidity shows just over 60% of the original D4 (Xu and Chandra, 1999: Figure 1). Soils tested in other conditions have missing time zero data points. But the hexane extraction process took over three hours. So, the time zero points are really somewhere between 0 and 3 hours. This would leave portions of D4 in contact with the soil surface until the HCl extraction step was initiated, at least 6 hours after the initial hexane extraction began. Without explicit values with times ascribed, it is difficult to accept the half-lives as reported. The latter problem demonstrates that there are in essence no time zero data in this study. Thus, the short half-lives ($t_{1/2}$ = of 0.04 d and 5.25d) could well be a result of the 3+ hour extraction time, poor solvent wetting of the soil surface, or the purging process.

Considering the information above, EPA should carefully consider the confidence placed in the soil dissipation rates reported in the DRE, and any data from these soil studies should be used to describe D4 dissipation, not degradation. Using these data to determine true degradation rates rather than dissipation (volatilization, irreversible sorption, as well as biotic and chemical transformation) may well underestimate D4 persistence in the environment.

The biodegradation section has only the following sentence: "Biodegradation occurs when an organic material is broken down by biological microorganisms under natural environmental conditions (i.e., aerobic and anaerobic)" (US EPA 2025g, 30). This section must be augmented. At a minimum, the assessment correctly states that D4 "does not undergo biodegradation in sediment under aerobic and anaerobic conditions and will have a strong affinity for organic carbon" (US EPA 2025g, 47). More information about biodegradation or the lack of it is needed in this section.

The *Draft Physical Chemistry and Fate Assessment for D4* contains the line, "In the environment, D4 is expected to transform into silanols and DMSD [dimethylsilanediol]" (US EPA 2025g, 49). The statement should be clarified with phrasing such as "…D4 is expected to slowly transform…" or "…minor fractions of D4 are expected to transform…"

The various documents within the D4 docket are replete with statements such as the following:

> When released directly to the atmosphere, D4 is not expected to undergo significant direct photolysis and will degrade slowly after reacting with photochemically produced OH. Due to its persistence in the atmosphere ($t_{1/2}$ > 2 days), D4 has the potential to undergo atmospheric long-range transport. (US EPA 2025g, line 1628)

And:

> Overall, D4 is not expected to be persistent in water and soil under environmentally relevant conditions but will be persistent in air and sediments." (US EPA 2025g, lines 1638–1639)

Even EPA's charge questions and public presentation during the SACC meeting repeatedly use the volatile nature of D4 as a reason for minimally considering dermal exposure. Yet, there are no measured atmospheric D4 concentrations provided for facilities that produce or utilize D4 in their manufacturing or shipping operations. So, conclusions about a lack of persistence in the air cannot be scientifically supported. This is a gross oversight and should have been part of the ECA or a more recent data requirement.

Recommendations

Short-term

- Clearly identify and explain exposure opportunities that are excluded from the *Draft Risk Evaluation for D4*.
- Remove/exclude discussion of risk management options in the *Draft Risk Evaluation for D4* and the associated assessment documents. If it is included, follow the hierarchy of controls.
- Add qualitative discussion of age-related differences for older adult women and the influence of weight loss/gain on exposure to D4.
- Reevaluate the soil persistence assessment to include acknowledgement that the assessment contains only one or two sets of D4 transformation data and that the soils from Hawaii and Michigan are not representative of soils commonly found in the United States.
- Use precise language that avoids blanket statements that cannot be supported by scientific principles or empirical data, especially when those blanket statements downplay exposures and risk.

Long-term

- Obtain needed release and use data for adequate exposure estimation.
- Develop scenario-based and probabilistic modeling capabilities to improve completeness of exposure opportunities included in assessments and provide ways to aggregate exposures from multiple sources.

Charge Question 1. Use of the D4 PBPK Model

Section 4.2.3 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.

Charge Question 1a

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

Scientific Rationale

Based on a rapid review of Section 4.2.3 of the *Draft Human Health Hazard Assessment for D4* (US EPA 2025f) and the supplemental *Draft Risk Evaluation for D4, Supplemental Information File: Evaluation of Campbell 2023 PBPK Model for D4* (US EPA 2025i), the 2023 Campbell D4 PBPK model seems to generally perform as intended when the model code, equations, and stated parameters are used to generate model outputs. The SACC arrived at this conclusion by considering two aspects. First, the structure and

mathematical implementation of the model reflect key toxicokinetic features of D4, including high lipophilicity, prolonged residence in adipose tissue, and the need to account for a mobile lipid pool (MLP). Second, when run with the listed parameters, the model reproduces the major time-course patterns of D4 concentrations observed in lab rats and human volunteers, including both the rapid initial decline and the slow terminal elimination phases. Therefore, the model seems sufficient to capture the dosimetric relationship between D4 intake dose and D4 plasma concentration in both rats and humans, and it is suited for interspecies extrapolation.

However, the SACC has two concerns regarding the use of the PBPK model:

First, the EPA evaluated the model primarily based on its ability to reproduce the time-course D4 concentration patterns observed in lab rats and human volunteers. One limitation is that the model is not assessed against absorption and clearance data *separately*. For instance, Section 1.2 of the *Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4) Supplemental Information File: Evaluation of Campbell 2023 PBPK Model for Octamethylcyclotetrasiloxane (D4)* (US EPA 2025i) reports percentages for absorption efficiencies (e.g., approximately 5 percent inhalation in animals; 6–17 percent in humans, 72–77 percent oral in rats, and 0.5–1.1 percent dermal), but these data were not used to evaluate the model's performance in reproducing the absorption process. Evaluating absorption and clearance separately is important because the model could overestimate both absorption and clearance, or underestimate both, and still produce the correct plasma concentration; in other words, the model's output could look accurate even though the underlying parameters are incorrect. Importantly, if absorption is overestimated or underestimated for a specific exposure route, then route-to-route extrapolation may not be reliable, even if other applications of the PBPK model, such as interspecies extrapolation, is still acceptable.

Second, the SACC questioned EPA's introduction of bidirectional multi-layer partitioning. This approach may be compensating for uncertainties or potential misspecifications in the fat-air partition coefficients. As noted in the supplemental materials "*Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4) Supplemental Information File: Evaluation of Campbell 2023 PBPK Model for Octamethylcyclotetrasiloxane (D4)* "(US EPA 2025i), Campbell and colleagues determined that earlier PBPK models tended to underestimate plasma concentrations of D4 because they overestimated clearance through exhalation. They attributed this to the earlier assumption of a *unidirectional* multi-layer partitioning (MLP), which increased the free D4 in blood and therefore allowed the system to "lose mass to exhalation too quickly." Their 2023 model addressed this issue by introducing a *recirculating, bidirectional* MLP. While this modification improved the model fit, the SACC raised the question of whether inclusion of an MLP, either unidirectional or bidirectional, is really necessary.

One reason for this concern is that the underestimation of plasma concentrations may alternatively reflect an underestimation of the fat-air partition coefficients used in the model. The model currently applies values of 100 for diffuse fat-air and 600 for distributed fat-air partition coefficients. Although these seem to be large, they may still be significantly below the values implied by physicochemical data. According to the *Draft Physical Chemistry and Fate Assessment for D4,* D4 has an octanol-air partition coefficient of at least $10^{4.22}$. According to Fremlin et al. (2021), D4 has a partition coefficient between

membrane lipid and octanol of $10^{-1.2}$ and a partition coefficient between storage lipid and octanol of $10^{0.13}$. As such, under equilibrium assumptions, these values imply fat-air partition coefficients on the order of 10^3 for membrane lipids and greater than 10^4 for storage lipids, which are substantially higher than the 100 and 600 currently used.

A closer examination suggests that the 100 and 600 values are not direct measurements but fitted parameters. As noted in the *Draft Human Health Hazard Assessment for D4*, many rat partition coefficients were optimized to fit inhalation data from Plotzke et al. (2000a) and then carried over to humans when direct human data were unavailable. Because these values were fitted before the bidirectional MLP concept existed, they likely represent a mixture of true partitioning behavior and other unmodeled uncertainties. The SACC noted that Campbell et al. (2023) themselves attempted to adjust partitioning and permeation parameters to address the slow terminal clearance phase, but the attempt was not successful. For example, Campbell and colleagues wrote:

> [W]e tested only adjusting parameters included in the Campbell et al. (2017) cyclic volatile methyl siloxanes (cVMS) model to capture the slower terminal phase clearance. This included attempts to reoptimize permeation coefficients and incorporating the deep blood compartment that is included in the D5 model; however, it was not possible to capture the terminal clearance without appreciably altering the model fit to short-term inhalation exposure or oral bolus data as the necessary alterations also affected the relationship between free D4 in the blood and the tissue deep compartments at the end of exposure and during the initial clearance phase (data not shown) (Campbell et al., 2023).

Since these data were not shown, it is currently difficult to evaluate whether the parameter adjustments they attempted were of a sufficient magnitude to test the physicochemical constraints suggested by measured partition coefficients. That is, we are not sure whether the underestimation of plasma concentrations can be resolved if the model developers had used values at the 10^3 and 10^4 magnitudes, rather than those of 100 and 600 as currently described in the *Draft Risk Evaluation for D4.*

Recommendations

- EPA should consider including additional model performance evaluation against absorption efficiency data, as listed in Section 1.2 of the supplemental PBPK Model Description and Review document, to better support route-to-route extrapolation.
- EPA should consider whether the reliance on a bidirectional mobile lipid pool may be compensating for uncertainties or potential misspecifications in the fat-air partition coefficients.

Charge Question 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.

General PBPK Model

In the *Evaluation of Campbell 2023 PBPK Model for D4,* the Committee found the historical overview to be an important addition (US EPA 2025i, 12). The description of the evolution of what seems to be a

single PBPK model—which the document consistently refers to as "the model"—would benefit from various suggestions that would provide clarifications and increase transparency and/or confidence in the model selection and use. These suggestions include:

- The Agency should better clarify in the document what is meant by "the model" and "the current version of the model," specifically whether the model is directly from Campbell et al. (2023) without modifications or if any refinements or improvements were made. Section 1.5 does not cite Campbell et al. (2023) as the "current" model – this needs to be clarified.
- Section 1.5 cites six studies used for PBPK modeling; the Agency should clarify whether these are all possible or proposed PBPK models for D4. It would be helpful if the Agency could also clarify whether these models were all generated or refined by the same research group or consortia, or if they represented efforts from a more diverse set of scientists, which would increase confidence.
- Although the discussion of the evolution of the model currently being applied is very helpful, it would be much clearer to incorporate a table of the various models, dates of issue, and some of their strengths and weaknesses, as well as improvements made.
- The Agency should consider adding a "methods" section for the support document generated in the September 2024 memorandum from ICF to EPA. Additions should include the approach for identifying and appraising existing models, as well as clarifying what was done in this revision of the DRE to support the Agency's assessment and to review the outcome (validation, assess the quality/reliability). Specifically, explain the methods used by ICF to assess the model's performance for internal dosimetry, species extrapolation, duration extrapolation, and POD derivation. It was not clear what statements were reported by the model authors versus assessed or run by ICF. It should be clearly stated how ICF selected the data used for evaluation and/or why these data are representative. For example, charts in Figure 4-2 were developed using the Campbell code, but the plots were not published by Campbell, which is confusing without a better description of what was done by ICF.
- Given the highly technical nature of PBPK modeling, as well as the overall importance of the model to the Agency's risk assessment, it would be helpful to understand the level of scientific expertise that ICF garnered in assessing the PBPK model. Since the Agency is relying on the contractor's assessment, the Agency should also be aware of any special experience and capabilities of the scientists conducting the review for the Agency, and this should be transparently provided in the support document.
- It is unclear why the support document contains a section on toxicity or regulatory history; these sections overlap, and some aspects potentially contradict that of other portions of the Agency's assessment. The Committee suggests omitting content that is not specific to the PBPK model in this document.
- Section 4.2 of the *Evaluation of Campbell 2023 PBPK Model for D4* presents an assessment of sensitivity, uncertainty, and variability. A general description of the approach and objectives for this assessment is needed. A variety of tables and figures are presented (see specific comments below), but it was difficult to understand the actual results for the analyses of the output as it relates to the inputs to the risk evaluation; that is, what are the

summary findings of "sensitivity, uncertainty, and variability"? It would be helpful to understand the impact of these sensitivities as it relates to the application in the risk assessment.

- Tables 4-2 through 4-6, while graphically interesting, were not informative as presented. The shading was difficult to differentiate; the key on Table 4-2 depicts high, mod, and low in the same shade. The impact of the sensitivity—e.g., if an icon has dark shading to indicate "high"—should be stated with respect to the predictions, along with the bounds/magnitude beyond 0.5; in other words, state what was the most sensitive.
- Figure 4-7 is helpful as a first step in understanding sensitivity, but the overlapping parameters are neither easily identified nor linked with the discussion.
- The document states in Section 4.2: "Using the values from McMullin et al. (2016) makes small but statistically significant differences in the sensitivity analysis and time-series results" (US EPA 2025i, 52). However, no data are provided to show this or to clarify the overall magnitude of the impact.

Internal Dosimetry

Strengths

It appears that the multi-compartment PBPK model for D4 has been improved over the years and that Campbell et al. (2023) recently incorporated the mobile lipoprotein pool into a bi-directional manner between liver and fat that improved predictions and better matches the human data.

The ability of the model to reproduce rat and human plasma kinetics and to reasonably track tissue distribution supports its use as a framework for estimating internal dose metrics such as area under the curve (AUC) in blood, which serve as the foundation for BMD modeling and POD derivation. The PBPK's capability of predicting systemic plasma concentration allows consistent translation and harmonization of internal doses across different exposure routes (respiratory, oral, and dermal exposures) and supports the route-to-route extrapolation.

The choice of dose metric for the POD, AUC of D4 in blood on the last exposure day, over a tissue-based dose metric appears to be appropriate, as data are available in both species to assess model performance.

Uncertainties

For a compound like D4, which has unusually high lipophilicity and very slow terminal elimination, small deviations in key parameters can produce large changes in predicted blood AUCs. Also, the conditions/assumptions for fitting may be different from the conditions/assumptions used in PBPK modeling. As such, this parameter sensitivity introduces uncertainty into internal dose metrics that serve as the basis for benchmark dose modeling and POD derivation.

The Committee also notes uncertainty surrounding the model's treatment of the mobile lipid pool. As mentioned in the Committee's response to charge question 1a, although the recirculating mobile lipoprotein pool improves model fit to observed plasma and fat data, it is not clear whether this construction reflects a true physiological process or whether it compensates for mis-specified partition

coefficients or other residual structural uncertainties in the model. The current fat-air partition coefficients, which were derived from data-fitting rather than direct measurement, appear to be several orders of magnitude lower than what would be expected based on reported octanol–air and lipid–octanol partitioning. If the true partitioning values are higher, the need for a mobile lipoprotein pool (and the degree to which it drives long-term clearance) may be reduced.

Animal-to-Human Extrapolation

Strengths

The ability of the model to reproduce rat and human plasma kinetics and to reasonably track tissue distribution supports its use as a framework for estimating internal dose metrics such as blood AUC, which serve as the foundation for BMD modeling and POD derivation. The model also applies species-specific physiological parameters, metabolic clearances, and partition coefficients to scale internal exposures across rats and humans. This biologically informed approach is superior to traditional default dosimetric adjustments, particularly for a compound like D4 with complex kinetics.

The application of the D4 PBPK model, which has been built on an extensive *in vivo* database covering the primary routes of exposure (i.e., inhalation and oral) in the animal bioassays, as well as the primary routes of exposure expected in humans (inhalation and dermal), reduces uncertainty in assessing risk from D4 exposure to humans over the default approach to assessing animal to human extrapolation.

Uncertainties

The Committee believes that the central source of uncertainty is the model's strong reliance on fitted parameters, particularly partition coefficients as mentioned in Committee's response to charge question 1a, that were optimized to match specific rat inhalation datasets rather than derived directly from measured physicochemical properties.

Route-to-Route Extrapolation

Strengths

The application of the D4 PBPK model, which has been built on an extensive *in vivo* database covering the primary routes of exposure (i.e. inhalation and oral) in the animal bioassays, as well as the primary routes of exposure expected in humans (inhalation and dermal), reduces uncertainty in assessing risk from D4 exposure to humans over a "default" approach to assessing route-to-route extrapolation.

The multi-compartment PBPK model for D4 has been improved over the years with Campbell et al. (2023) incorporating mobile lipoprotein pool into a bi-directional manner between liver and fat that improved predictions that better match the human data (Utell et al. 1998).

Uncertainties

As mentioned in the Committee's response to charge question 1a, the Agency evaluated the model primarily based on its ability to reproduce the time-course D4 concentration patterns observed in lab rats and human volunteers, but it did not evaluate the model against absorption and clearance data separately. Evaluating absorption and clearance separately is important because the model could

overestimate both absorption and clearance, or underestimate both, and still produce the correct plasma concentration level. However, if absorption is overestimated or underestimated for a specific exposure route, then route-to-route extrapolation may not be reliable.

Because the model inherits parameter values fitted to rat data, it may inadvertently carry over rat-specific artifacts when used to estimate human kinetics. The scarcity of long-term human toxicokinetic data, particularly for repeated or continuous exposures, limits the ability to verify the model's predictions in humans. As a result, the internal dose metrics generated for humans may not fully reflect human-specific metabolic capacity, fat distribution, or interindividual variability. These limitations are especially relevant given the model's role in replacing default uncertainty factors for interspecies differences.

With respect to route-to-route extrapolation, significant uncertainty arises from the dermal exposure component. Empirical data demonstrate highly variable dermal absorption and exhalation profiles across human studies, and the model underpredicts exhaled concentrations in at least one dataset. Because the dermal module is not parameterized with the same depth of data available for inhalation and oral routes, the reliability of dermal HEDs is less certain. For exposure scenarios where dermal absorption is a major contributor, this uncertainty may influence the accuracy of internal dose estimates used for risk characterization.

Section 4.3 of the *Evaluation of Campbell 2023 PBPK Model for D4* indicates the model performance for oral exposure cannot be assessed (US EPA 2025i, 52), yet Section 5 concludes that the model is sufficient for risk assessment and can be used for common routes of exposure (US EPA 2025i, 53). It would be helpful if the discrepancy were addressed and syntheses from the sensitivity analyses were incorporated to describe confidence and uncertainty in using the model for the oral route. It would also be helpful to describe the suitability or lack of suitability of the model for oral exposure. Similar statements regarding species extrapolation, the dermal route, and temporal components would be helpful as well.

Duration Extrapolation

Strengths

The PBPK's representation of the slow elimination phase from adipose tissue helps approximate the cumulative internal burden under repeated exposures. While long-term human data remain limited, the model's ability to simulate continuous exposure scenarios provides a practical tool for estimating steady-state internal doses in humans.

Uncertainties

The model predicts long-term internal burdens based on repeated-dose simulations, but these projections depend heavily on how accurately the model characterizes the slow release of D4 from adipose tissue. Without empirical long-duration human data to validate these outputs, estimates of body burden under chronic exposure scenarios remain uncertain. If adipose partitioning or clearance is mis-specified, the model may overestimate or underestimate the degree of accumulation and therefore the internal doses driving POD calculations.

POD Derivation

Strengths

The PBPK-generated POD can be translated into human-equivalent concentrations (HECs) and HEDs that incorporate species differences in absorption, metabolism, distribution, and elimination. This avoids reliance on default uncertainty factors to account for interspecies differences because the scaling is explicitly modeled. This improves scientific transparency and can reduce uncertainty in the final risk evaluation.

Recommendations

- The Agency should explicitly specify whether the model is directly from Campbell et al. (2023) without modifications or if any refinements and improvements were made. Section 1.5 does not cite Campbell et al. (2023) as the "current" model – this needs to be clarified.
- The Agency should consider the addition of a methods section for the support document generated by ICF, including the approach for identifying and appraising existing models, as well as clarifying what was done in this document to support and review the Agency's assessment and to evaluate the quality of the risk evaluation. The experience and capabilities of the ICF scientists conducting the review should be included.
- Internal dosimetry – Although the recirculating mobile lipoprotein pool improves model fit to observed plasma and fat data, it is not clear whether this construction reflects a true physiological process or whether it compensates for mis-specified partition coefficients or other residual structural uncertainties in the model. The current fat-air partition coefficients, which were derived from data-fitting rather than direct measurement, appear to be several orders of magnitude lower than what would be expected. This needs to be expanded and clarified in the document.
- Animal-to-Human Extrapolation – The document should address the uncertainty from the model's strong reliance on fitted parameters, particularly partition coefficients as mentioned in Committee's response to charge question 1a, that were optimized to match specific rat inhalation datasets rather than derived directly from measured physicochemical properties.
- Route-to-Route Extrapolation – The Agency should evaluate absorption and clearance separately because the model could overestimate both absorption and clearance, or underestimate both, and still produce the correct D4 concentration in plasma. If absorption is overestimated or underestimated for a specific exposure route, then route-to-route extrapolation may not be reliable.
- Section 4.2 of the *Evaluation of Campbell 2023 PBPK Model for D4* presents an assessment of sensitivity, uncertainty, and variability. A general description of the approach and objectives for this assessment is needed.

Charge Question 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.

Response

The PBPK model used various parameters to determine evaporation from the skin and absorption into skin and transport into blood from skin. These dermal parameters were based on a "human *in vivo* dermal absorption study using C13-labeled D4 (Plotzke et al., 2000b), and an *in vitro* evaporation experiment." (*Human Health Hazard Assessment (*HHHA) lines 2226 -2229 and Draft Risk Evaluation 2342- 2345).

The Campbell Model simulations (Campbell et al. 2023), using inhalation and oral routes in rats and inhalation, oral, and dermal routes in humans, plausibly predicted D4 concentrations in exhaled breath and plasma/blood for both inhalation (Utell et al. 1998) and dermal exposure routes in humans (Plotzke et al., 2000b).

The use of human data increases the sensitivity of the model used for dermal absorption. Specifically, results of the Campbell model compared to experimental human dermal exposure results from both Plotzke et al., 2000b, as cited in Reddy et al., 2007) and Biesterbos et al. 2015 appear to provide a useful, if uncertain, estimate of dermal absorption. Given the low levels of exposure generally observed by the dermal route, this uncertainty may not unreasonably affect the results of the risk evaluation.

According to EPA (US EPA 2025i, 34), the PBPK model slightly overestimates dermal exposure compared to the Reddy et al., 2007 data (as reported by Plotzke et al. 2000b) and substantially underpredicts the experimentally derived values from Biesterbos et al. 2015. However, despite the underprediction of the Biesterbos experimental results, both the EPA and Biesterbos note that the post-exposure concentrations in Biesterbos did not exceed background levels. Biesterbos concluded: "Overall, the results of our study indicate that the dermal absorption of D4 and D5 contributes only marginally to internal exposure following dermal applications" (Biesterbos et al. 2015, 231). These data therefore indicate that exposure and absorption through the dermal route is likely to be low but uncertain.

In addition to the limited data for D4, it should be noted that dermal absorption of virtually all compounds generally exhibits large variations by anatomic region. In a systematic review by Feschuk et al., (2022 that addresses this phenomenon in *in vitro* human models, it was concluded that

> Eight relevant articles were identified, which together, explored 15 anatomic regions. Four studies compared percutaneous absorption between scalp and abdominal skin, and all concluded that the former was more permeable. Within those 4 studies, 10 penetrants of varying physical/chemical properties were tested, suggesting that anatomical location has a greater effect on percutaneous absorption than the penetrants' properties. (Feschuk et al.,2022)

While it may not be possible to more precisely estimate dermal absorption, the extent of this uncertainty and the reality of large variations in absorption for different regions of the body should be acknowledged. This depends upon where the exposure would take place on a human body for the various exposure scenarios. This is an important consideration given the extent of D4 or D4 containing

mixtures in PCPs and multiple household utensils. Consideration and discussion of this variability factor should be included in the EPA's analysis.

Consistent with comments regarding the importance of noting all potential sources of variability, in the final *Model Applicability* conclusions, the EPA (2025i, 52) notes that the current model uses data wherein relatively significant amounts of D4 were measured in exhaled breath of human subjects after a dermal exposure. In contrast, a similar study showed no significant amount of D4 observed in the exhaled breath (Biesterbos et al. 2015). According to EPA,

> The difference in the results may be due to different exposure scenarios. Plotzke et al. (2000b) [as cited in Reddy et al. (2007)] applied 1 to 1.4 g of D4 to the two axillae, whereas in Biesterbos et al. (2015), 2.5 mg of D4 per cm^2 were applied to the forearm for 1 hour to achieve an accumulated exposure of 15 mg/cm^2. Therefore, the dermal model should be used with caution. (US EPA 2025i, 52).

It should be noted that if a surrogate of the human skin surface area of the adult hands from the EPA's Exposure Factors Handbook is used for comparison to the surface area of the two-axilla studied in Reddy et al. 2007, the approximate surface area would be in the range of 890 to 1,070 cm^2. If 1 to 1.4 g (1,000 to 1,400 mg) of D4 was applied to this surface area, this application would be equivalent to approximately 0.9 mg to 1.3 mg/cm^2, which is approximately an order of magnitude lower than the application amount reported for the Biesterbos et al. 2015 study. The EPA could note this dosing discrepancy and other study variabilities more explicitly, as it appears that the study with a lower overall dose resulted in higher amounts of D4 in exhaled breath. It also appears from the Reddy et al. (2007, 428) study that shaving of the underarms by some fraction of the female participants prior to the application of D4 influenced the skin condition compared with the male participants and resulted in a systemic dose in females that was 2.5 times higher; it is unclear the extent to which this factor influenced the overall study results when compared to the Biesterbos study (Reddy et al., 2007). Given the low overall dermal exposures observed in both studies, the EPA could consider revisiting this statement in the Supplemental Information File to clarify the nature of the uncertainties inherent in the data being used in the risk evaluation.

In reality there are two "Plotzke et al. (2000)" papers: one for rats (Plotzke et al. 2000a) and the other for humans [i.e., the one "as cited in Reddy et al. (2007)" mentioned in the EPA document] (Plotzke et al. 2000b).These appear to have been collapsed into a single citation (only the rat study), and the EPA seemed to mistake the human paper for the rat paper (e.g., in the captions of Figures 4-3 and 4-4). Also, the EPA had two PBPK models, one for rats and the other for humans. The EPA explicitly tuned/calibrated/adjusted the rat model, using rich rat datasets, including the Plotzke rat paper. Once they had confidence in the rat model, they created a human copy by replacing rat physiology with human physiology (from Brown et al., 2016), extrapolating rat-specific chemical properties to human-specific values (or just assumed they are the same for both rats and humans), while keeping the same compartments and equations. The human model was *not* tuned to human data.

The Plotzke human paper and the Biesterbos paper were actually used for independent evaluation of the human model's predictive performance. The evidence for such an independent evaluation is that the human model underpredicted the measurements in the Biesterbos paper (Figure 4-4).

Another potential variability that the SACC has repeatedly advised the EPA about is the likely dissolution of volatile chemicals in perspiration or sorption to skin surfaces, thereby increasing dermal uptake. It is unclear if this variability has been explicitly considered.

Additionally, it is important to provide an overview of how EPA derived the dermal POD with the assistance of the PBPK model. EPA derived the dermal POD by calculating BMDs with a human-parameterized PBPK model using dermal studies conducted under *unoccluded* conditions. The PBPK model explicitly integrates dermal absorption and skin-surface evaporation of this volatile chemical. For scenarios where *occlusion* may limit evaporation (e.g., clothing/bedding), EPA scaled those HEDs by "a ratio" that reflects the difference between occluded versus unoccluded absorption rates (US EPA 2025h, 143). Because the BMD/POD already reflects absorption and evaporation, EPA compares applied dermal doses (not further adjusted) to that dermal POD when calculating MOEs.

For this reason, multiple Committee members identified the following uncertainties:

- Generally speaking, for highly volatile, hydrophobic chemicals like D4, even basic property values (water solubility, partition coefficients, Henry's Law constant) have documented measurement challenges; those propagate into evaporation/partition terms at the skin-air interface. As such, the SACC recommends carrying these uncertainties explicitly into the dermal POD via Monte-Carlo or bounding analyses.
- For human modeling, the PBPK dermal sub-model evaluated against a single human study (i.e., the Plotzke and Biesterbos datasets). Such independent evaluations indicate that the model underpredicted the Biesterbos dataset. In the animal model, rate constants for skin absorption and other skin-related parameters were "visually optimized" based on these limited data (US EPA 2025h, 27, Table 3-3). While the skin absorption permeability seems to fall within the higher end of the plausible range (for the plausible range, see Brown et al. 2016, Figure 4), using these values may raise identifiability and transferability concerns across sites, doses, and formulations. As such, the SACC recommends documenting the derivation and performing a scenario-based sensitivity analysis on that ratio.
- The SACC believes that EPA appropriately used the PBPK model to derive dermal HEDs under *unoccluded* conditions because D4 volatilizes rapidly from skin. For occluded use-cases, EPA scaled those HEDs by "a ratio" (US EPA 2025h, 143) that reflects the difference between occluded versus unoccluded absorption rates. However, neither the *Draft Risk Evaluation for D4* nor the *Evaluation of Campbell 2023 PBPK Model for D4* shows a derivation, dataset, or calculation for that occlusion adjustment ratio. The EPA simply states that such a ratio was applied, rather than providing the basis of that ratio. The value used appears to be approximately 0.55, as the SACC inferred this from the 4 HEDs reported in the *Draft Risk Evaluation for D4*: unoccluded = 394 (acute) and 326 (intermediate/chronic); occluded = 216 (acute) and 179 (intermediate/chronic). (US EPA 2025h, 167). In particular, the evidence basis, and bounds for that ratio are pivotal, as if the occlusion factor is mis-specified, internal dose could be over- or under-estimated. It is very confusing that the EPA does not detail this part for transparency and clarity. The SACC recommends identifying the underlying data and method for deriving this occlusion adjustment (e.g., human dermal datasets, *in vitro* skin

studies, or model scenarios) and clarifying whether a single constant was applied across different conditions (e.g., durations and life stages).

- It is unclear the extent to which bedding or clothing would actually create occluded conditions consistent with an immersion scenario, for example. The EPA should provide the rationale for this assumption.

Dermal Exposure Assessment for D4

Regarding EPA's dermal exposure assessment for D4, according to the EPA's *Draft Environmental Release and Occupational Exposure Assessment for D4*:

> Dermal exposure data were not reasonably available for the COUs in the assessment. Because D4 is a volatile liquid that readily evaporates from the skin, EPA estimated dermal exposures using a variation of Dermal Exposure to Volatile Liquids Model and the EPA 2-Hand Contact with Container Surfaces Model. The model was used to calculate the applied dose of D4 to the skin (i.e., the amount available for absorption rather than the amount absorbed). Evaporation and absorption were not included in the dermal exposure model because parameters related to D4's evaporation from and absorption through skin were included in the PBPK model used to estimate dermal hazard values (i.e., acute and intermediate/chronic human equivalent doses). The dermal parameters included in the model are based on a human *in vivo* dermal absorption study and an *in vitro* evaporation experiment. The resulting HEDs used to calculate occupational risks are specific for unoccluded scenarios (where D4 is not trapped at the skin surface). A more detailed explanation of this can be found in Section 4.2.2 of the *Draft Human Health Hazard Assessment for Octamethylcyclotetrasiloxane (D4).* (US EPA, 2025e, 31).

However, evaluating or estimating dermal exposure of volatile substances without considering evaporation is not appropriate for a refined risk determination, regardless of the dermal hazard values determined, and is also important given the need to consider aggregate exposures. The Dermal Exposure to Volatile Liquids (DEVL) model uses an estimated weight fraction of a substance on the surface of the skin and an estimated percent absorbed of that substance. The model does not assume any evaporation from the skin surface for the substance being evaluated. However, such an approach does not appropriately characterize exposures in real world scenarios, particularly for substances such as D4, which are volatile. According to Frasch et al. (2013, 2), the "apparent simplicity [of the fractional absorption model] is belied by complicating factors. It has been observed that an inverse relationship often exists between dermal loading and fractional absorption" and further, "[a]s the loading increases, the fraction of chemical that is absorbed diminishes. Thus, the fractional absorption factor is not a constant for a given chemical, and it is typically highest for low dermal loads that are characteristic of environmental and occupational exposures."

Using a fractional absorption model can either overestimate or underestimate dermal uptake potential. These types of screening-level or Tier 1 models therefore introduce substantial uncertainty into the dermal exposure assessment. Instead, as previously discussed in comments provided to EPA by the SACC, an approach should be considered that evaluates both the absorptive and evaporative flux of the substance of interest into and out of the skin. The Agency states that

> In the case of D4, the hazard value (i.e., HED) was calculated using a PBPK model which accounted for the absorption that would occur during dermal exposure events. Therefore, EPA calculated dermal

> exposure estimates using an applied dose of D4 occurring during a dermal exposure event. This means that the fractional absorption value is 1. (US EPA 2025e, 204).

However, it is not physically possible that 100 percent of an applied external dose of D4 will be available for absorption into the skin, given its volatility. It is unclear what the actual effects of this assumption are on the ultimate risk assessment decisions made by the EPA for D4, and the Agency should clarify and support the basis for this assumption in their risk evaluation documents. An alternative approach to the DEVL model that the EPA could use to more reasonably address the evaporative flux of D4 can be found in the American Industrial Hygiene Association's textbook (Anthony et al., 2009, 115); specifically in equations 13-21, 13-22, and 13-23 under the section "Fraction of dermal absorption of a volatile liquid deposited on the uncovered skin". These data can then also be used to estimate concomitant inhalation exposure for the exposed individual and those nearby.

In the EPA's 2-Hand Contact with Container Surfaces Model, the default dermal loading values used are not specific to volatile liquids. According to the EPA's guidance for the Chemical Screening Tool for Exposures and Environmental Releases (ChemSTEER) model, it is noted that "Selected ranges of 'Q' values for liquid handling activities taken from (ChemSTEER, 2000). According to this report, referred to hereinafter as Cinalli et al. 1992, six liquids were initially selected for the study of liquid retention on the skin, but three of these were omitted from the analysis because "an acceptable experimental procedure to address volatilization/evaporation losses could not be developed for them" (Cinalli et al. 1992, 8). The three liquids ultimately used in the study included mineral oil, cooking oil, and bath oil. None of these three liquids have physical-chemical properties that are similar to D4. The values of 1.4 mg/cm^2 and 2.1 mg/cm^2 come from initial wipe sample measurements to measure retention on the skin for these three oils following application to the skin surface (rather than incidental transfer). The value of 10.3 mg/cm^2 comes from the maximum value for immersion of the skin in these three oils (range 5.9 to 10.3 mg/cm^2) (Cinalli et al. 1992). In 2018, the Netherland Organisation for Applied Scientific Research reported as part of an evaluation of dermal factors for its "Dermal Advanced REACH Tool" (dART) model that, "[v]arious experimental studies found that increasing viscosity (and stickiness) resulted in significant higher dermal exposure (Gorman et al. 2012; Cinalli et al. 1992)" (Goede et al. 2018). Aside from specific circumstances such as direct immersion of skin into highly viscous liquids, 2.5 mg/cm^2 appears to be a reasonable upper-bound estimate for dermal loading of liquids in real-world exposure scenarios (Phanprasit et al. 2019; Creta et al. 2018; Galea et al. 2014; Urbanus et al. 2014; De Vries 2012; Christopher et al. 2011; Cherrie and Semple 2010; De Fent et al. 2009; Bello et al. 2008; Fent et al. 2008; Chang et al. 2007; Semple et al. 2007; Fent et al. 2006; Lindsay et al. 2006; Pronk et al. 2006; Vermeulen et al. 2006; van Wendel de Joode et al. 2005a; van Wendel de Joode et al. 2005b; Eriksson and Wiklund 2004a, 2004b; Gijsbers et al. 2004; lgado et al. 2004; Roff et al. 2004; Garrod et al. 1999; Roff 1997). However, this value is not specific to volatile liquids. The EPA should seek data from the stakeholders to better understand the specific loading characteristics of D4 and how this value compares to the values in the literature and the 2-Hand Contact with Container Surfaces model.

Regarding the factors considered in determining acceptability of risk for D4, the EPA made assumptions about the effectiveness of gloves in a wide variety of OESs for this risk evaluation and used these assumptions to assess the acceptability of the exposure scenarios evaluated. Specifically, the EPA stated

that it had determined protection factors (PFs) for glove use in the risk evaluation and reported that "It should be noted that the described PFs are not based on experimental values or field investigations of PPE effectiveness, but rather professional judgements used in the development of the ECETOC Targeted Risk Assessment model. EPA did not identify reasonably available information on PPE usage to corroborate the PFs used in this model." (US EPA 2025e, 35). As noted in previous SACC comments, PPE such as gloves are considered the least desirable control in the hierarchy of controls. Please see the comments that the SACC provided in its report on phthalates prepared earlier this year. Additionally, it is unknown if EPA received information describing other available controls for the OESs evaluated, and if any other controls were available or present to reduce or limit exposures. These controls could substantially affect worker, ONU, and general population exposure for each OES, and will affect the similar exposure groups determined and potentially also the risk evaluation determinations.

Recommendations

- While the levels of absorption generally observed by the dermal route specifically appear to be low based on both the PBPK model output and the limited available empirical human health *in vivo* data, the discussion by the EPA of the potential sources of uncertainty regarding use of this approach should be expanded and clarified.
- Consider an alternative approach to the DEVL model for a refined risk determination to account for the evaporative flux of D4 from the skin; see the American Industrial Hygiene Association's *Mathematical Models for Estimating Occupational Exposure to Chemicals* (Anthony et al., 2009), as noted above, especially equations 13-21, 13-22, and 13-23.
- EPA should consider using more relevant values for Q, or skin loading. The current values being applied are not specific to volatile liquids or to the general properties of D4.
- EPA should provide additional rationale and support for the assumptions around the occluded dermal exposure scenarios applied in the risk evaluation.
- When referring to human dermal exposure data, the citation "Plotzke et al. (2000)" should reference the following EPA internal report: Plotzke KP, Utell MJ, Looney JR (2000) Absorption, Distribution and Elimination of 13C-d4 in Humans after Dermal Administration. Report No. 2000-I0000-49147. 2000-09-19. Rochester, NY: University of Rochester Medical Center. (Plotzke et al. 2000b). The current reference to the paper (HERO ID 6833981) is incorrect.

Charge Question 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.

Response

With respect to technical comments, the Committee offered comments in two general areas: (1) internal validity aspects relating to the PBPK model's ability to act as a representation for children-specific AUC; and (2) "external validity" aspects relating to the applicability or generalizability of the PBPK approach to the COUs. Regarding generalizability, the Committee specifically commented on the application of the adult model to adjust blood AUC from a two-generation rodent study wherein blood AUC is being transformed from a study involving pregnancy models, as well as on limitations in the model (and general assumptions of exposure in selected COUs) for human use, including dermal exposures in children via PCPs as well as potential impacts of the use of birth control on PBPK parameters. These are further described below.

The core uncertainty that the SACC identified is that the PBPK model was parameterized for "non-pregnant" adults, which does not include child-specific parameterization, pregnancy, aging, or model validation. In particular, the PBPK report emphasizes D4's unusual toxicokinetics (such as the lipoprotein-associated pools and deep fat compartments included by Campbell et al. 2023; see the SACC's response to charge question 1a). It is legitimate to expect that age-dependent differences in lipid handling and tissue fractions could alter internal AUCs for children relative to adults. However, the model supplies adult parameters, and no child-specific evaluation is shown. Of note, the closing statement of the support document in the conclusions reads, "…but it has not been tested on pregnant women, infants, or the elderly" (US EPA 2025i, 53). The prior paragraph indicates that age is an important parameter impacting cardiac output (and concordantly, tissue volume, tissue uptake, etc., to change with age) and that "additional modifications need to be made to account for those factors" (US EPA 2025i, 53). It is unclear why the EPA (or their contractor) have not themselves carefully investigated these aspects, given clear acknowledgements of the model applicability limitations.

The SACC also noted that one of the public commenters from Ramboll – the authors of the PBPK model – indicated that, "While the human D4 PBPK model is based on data collected in adults, extrapolation to children does not inherently increase uncertainty given that D4 is a volatile compound with low solubility in blood and rapidly exhaled. More extensive evaluation and incorporation of the ontogeny of the cytochrome P450 enzymes (CYPs) involved in D4 metabolism in the D4 PBPK model could further decrease uncertainty in application of the risk evaluation in children." While the rationale provided by these public commenters is insufficiently robust to address the charge question (e.g., does not address other aspects of PESS, such as pregnancy and sensitive life stages, which are more directly related to application of the modeling data to data from the two-generation study), it is reasonable that the Agency could consider further assessing these aspects as starting points to address uncertainty for the application to children.

When considering pregnancy specifically, some SACC members also questioned how the PBPK model would behave for women who are using birth control medications. The mechanisms of action involved with physiological effects of D4 will be discussed in more detail later in this report and highlight the endocrine disrupting effects of D4 exerted on estrogen sensitive systems. Most birth control medications deliver hormones in a way that mimics pregnancy by inhibiting ovarian cycles and ovulation. In such cases, *all* women of reproductive age who are using birth control will be inadequately covered by such a

model. This lack of health protectiveness is concerning given the next charge question, which addresses the inhalation POD that is based on decreased litter size for rodents.

The SACC also noted the importance of considering obesity in PBPK modeling. With almost 40 percent of the US population obese or overweight, it is important to consider obesity as a parameter when evaluating toxicokinetics of D4. Individuals with higher-than-normal body fat will have a different toxicokinetics and possibly higher internal dose. This is further complicated by the fact that several responses associated with estrogen and other hormones are different in obese individuals, which can affect D4's proposed mode of action and POD.

The SACC offered many comments that address the applicability of the model for risk evaluation. First, with respect to the outcome of the application of the model: human hazard assessment has focused on reproductive effects for the health-based benchmark. While there is still uncertainty related to the MOA for any health effect, the general absence of developmental effects in guideline studies generically informs potential uncertainties related to use of the PBPK model for children. That is, if developmental effects are generally not observed, and D4 is not genotoxic, the hazard data do not suggest a particular health-based sensitivity in children. Rather, the toxicity data relied upon by the Agency are based on reproductive effects—and generally, inherent in the risk assessment process and selection of the most sensitive endpoint, the health-based benchmarks are meant to be protective of any non-cancer effect. Collectively, this reduces uncertainty in applying the PBPK model to children in context of the risk evaluation—that is, the generalizability or external validity of the model (recognizing, however, this does not reduce potential uncertainty around HECs for children that are dependent on the model; i.e., the internal validity OR the uncertainty of using an adult model to estimate HECs in a pregnancy model).

With respect to uncertainty factors, the SACC noted that because the D4 PBPK model already "accounted for interspecies toxicokinetics" (US EPA 2025h 168, line 3391), the EPA used interspecies uncertainty factor (UF_A) of 3 (rather than the traditionally used factor of 10) "to account for any toxicodynamic differences across species" (US EPA 2025h, 168, line 3392). In addition, EPA used a default intraspecies uncertainty factor (UF_H) of 10 "to account for both toxicokinetic and toxicodynamic variation in sensitivity within human populations" (US EPA 2025h, 168, lines 3395-3396). It is not clear whether the EPA intends to use the UF_H=10 to account for the toxicokinetic differences between children and adults (so that EPA believes the issue listed on charge question 1d is already solved). If so, the EPA should make this point clear within the *Draft Risk Evaluation for D4*. EPA should more clearly state the extent to which these UFs could reasonably address uncertainty in using the adult model to estimate D4 behavior for PESS.

Although overlapping with other charge questions, it was also noted that one of the major uncertainties identified when applying the PODs to children is that EPA excluded the use of PCPs as a route of exposure. PCPs include products such as skin cream, lotions, shampoos, and conditioners. PCPs could result in exposure via dermal or inhalation routes. This likely reflects a major route of exposure for children, and so by excluding PCPs, EPA is underestimating the aggregate risk. In that regard, it is inappropriate for EPA to exclude children younger than 11 years from dermal exposure calculations, as it is highly likely that they would be passive users of PCPs as well as exposed to aerosolized D4. This

concern is also the same for acute inhalation exposure; children under 10 years should be modeled as product users like young teens and adults, since they could be exposed though acute inhalation exposure via scents from PCPs. This is contrary to EPA's current approach of modeling children younger than 10 as bystanders only. A strength regarding the assessment of dermal exposure is that EPA considers different durations of sleep for different age groups (i.e., separating out infants) when assessing dermal exposure.

Recommendations

Given the importance of the PBPK modeling on the risk evaluation, the SACC has two key recommendations to better address the uncertainty related to use of a PBPK model designed for non-pregnant adults to predict D4 behavior in women of reproductive age and children:

- Conduct a sensitivity analysis—even if it is qualitative—to address parameters and potential direction of output (over- or under- estimates of AUC) that would or could be different if the model were applied to (1) children; and (2) pregnant women. Generally, it is expected that an assessment of the parameters in context of life stage/children would have already been conducted by EPA (or the ICF contractor) as part of the model assessment. At a minimum, it would be helpful to have a qualitative characterization of which parameters would be subject to changes in children and pregnant women, along with discussion of these parameters in context of the sensitivity analyses.
- State whether parameters that would change/have highest uncertainty for these PESS also the parameters of highest sensitivity in the model.
- To the extent possible, the sensitivity analyses should consider obesity, including potential exacerbating effects of weight loss drugs that could also induce rapid release of other fat stored chemicals.
- Provide specific discussion in the risk evaluation regarding the intentions of the inter- and intra-species uncertainty factors to address this issue of using an adult PBPK model to inform the health-based benchmark used in assessment of COUs for children.

Overarching Recommendation Across Assessments

The SACC offers comments to EPA regarding PBPK modeling in EPA's future risk assessments, for all lipophilic chemicals not specific to D4.

The SACC highlights the need to represent mobilization of environmental toxicants during rapid weight loss (e.g., through weight loss drugs, programs, or periods of illness). For lipophilic chemicals that are stored in adipose tissue, rapid lipolysis can release the stored fraction of chemicals residing in adipose tissue to the bloodstream. If the body does not efficiently eliminate these toxicants from the bloodstream, this may transiently increase blood and target-organ concentrations even if external exposure is unchanged (Jandacek et al. 2024; Lee et al. 2018; Li and Wania 2017). This remobilization can (1) produce short-term internal dose spikes in contaminants (likely a mixture of chemicals); (2) bias steady-state assumptions used in POD extrapolation and MOE calculations; and (3) elevate secondary transfers (e.g., to breast milk) and co-exposures with weight-loss medications.

In addition, EPA's PBPK modeling should explicitly consider people with obesity or who are members of Indigenous populations, especially those in colder climates who tend to have higher basal body fat. For lipophilic chemicals, obesity can meaningfully change internal dosimetry via: (1) a larger adipose compartment, which alters volume and distribution of chemicals and potentially prolongs elimination half-life; (2) higher circulating lipoproteins and an expanded lipid-associated pool (MLP), possibly changing blood/tissue partitioning; (3) obesity-related physiology with a shift in clearance and route-to-route equivalence; and (4) dermal and inhalation exposures, which may scale differently with body size, skin surface microenvironments, and activity patterns. Without an obesity parameterization, adult "central" models are likely to under- or misestimate AUCs and peak concentrations for this subpopulation of obese individuals. In addition, responses associated with estrogen and other hormones differ in obese individuals, which can affect D4's proposed MOA and POD. In addition, in the specific D4 case, Indigenous populations also rely on sustenance fishing, which can be a major dietary exposure in case of D4. It is possible that these communities have a higher internal dose due to higher fat and increased storage of D4. In the cases of arctic and sub-arctic indigenous populations, fat composition those people needed to weather cold temperatures coupled with the practice of blubber consumption could increase D4 exposures for this PESS population.

In future assessments of lipophilic chemicals, the SACC recommends that the EPA more fully and carefully consider obesity and weight-loss trajectories in chemical toxicokinetics, at least in sensitivity/bounding analyses for potentially exposed or susceptible subpopulations.

Charge Question 2. Human Health Hazard Assessment

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

Charge Question 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.

General Comments

There is a large literature that links adverse effects of D4 (generally inhalation) exposure to adverse reproductive outcomes, particularly in females; males do not show a similar extent of adverse effects. These effects center around female reproduction, including estrous cycle disruption, and a reduced number of implantations and live births. Experimental designs included various ages. There were studies in both in humans and rodents.

The *Draft Human Health Hazard Assessment for D4* provides an overall summary of inhalation studies:

> Across studies and endpoints with multiple concentrations, most reproductive effects resulted in NOAECs [No observed adverse effects concentrations] of 3639 mg/m3 (300 ppm) and LOAECs [lowest observed adverse effects concentration] of 6066 mg/m^3 (500 ppm) (as nominal values). Supporting

> studies that evaluated single D4 air concentrations often identified reproductive effects at the nominal concentration of 8492 mg/m^3 (700 ppm). EPA selected the inhalation reproductive toxicity study by WIL Research (2001a) as the basis for dose-response because it had a high overall quality determination. (US EPA 2025f, 11–12)

Exposure to D4 by inhalation in two-generation studies is the basis for selection of decreased live litter size as the health effect for dose-response modeling and derivation of the POD. Decreased live litter size was observed at exposures of 500 ppm and 700 ppm; other effects, such as estrous cycle perturbation and reduced fertility indices, were observed at lower exposures (concentrations) (WIL Research 2001). However, the variation in response is substantial and the $BMDL_{05}$ accounts for this. The POD is much lower. A spatial comparison (e.g., via a scatter diagram) of the $BMDL_{05}$ with other NOAECs and LOAECs should help provide a clearer view of the utility of the POD.

Silicone polymers that may contain residual amounts of D4 are used in biomedical applications, pharmaceuticals, in certain pest control products, and in industrial processes as surfactants (detergents) and defoamers (anti-foaming agents). They are also used in lubricants, cleaning products, sealants, adhesives, waxes, polishes, and coatings.

D4 is a component of the substance cyclomethicone. D4 is used in cosmetics and other PCPs available to consumers. At the time of the assessment, products such as hair and skin care products, antiperspirants and deodorants contained D4. Although EPA considered the use of many of these products as outside the purview of this D4 evaluation, the Committee emphasizes that these products will contribute D4 to the environment (air, water, soil) from their disposal. EPA's landfill assessments stop short of a more robust assessment of landfill's contribution to aggregate airborne D4 exposure.

Most studies utilized inhalation as a method of exposure to known concentrations with reproductive effects being primary effects noted (Matthews 2021; Meeks et al. 2022; Marrugo-Padilla et al. 2024). The experimental data also show effects on other organs, including liver, suggesting that these measures may be reliable indicators of exposure and effects.

In studies used to establish the inhalation POD, 700 ppm appears to be the exposure concentration that elicits repeatable significant adverse reproductive effects in females. The WIL Research (2001) study showed multigenerational effects; clarification is needed to follow the treatment sequence across generations. Presumably, the female offspring receive the same treatment as their mothers, although there is a mention of exposure through lactation only (see EPA 2025f, 12). If lactation is the sole exposure route, then it is difficult to assess the extent of D4 exposure experienced by neonates.

More importantly, reduced litter size is a strong indicator of overall reproductive impairment in the female, albeit rather a downstream measure. As such, it is unlikely to be sensitive and would require sufficient sample size for reliable detection of effects. The EPA may consider using other, more sensitive, measures. Differences in the induction of the preovulatory luteinizing hormone (LH) surge in rodents and humans (Dekant et al. 2017) should be considered if molecular measures are selected.

In males, the WIL Research (2001) study authors reported the NOAEC from their study was 250 ppm in air based on effects on male epididymal, prostate weight, thymus weight, and kidney mineralization with a NOAEC of 100 ppm in air where these effects were no longer observed. Additional studies found that

males primarily showed liver and liver enzyme cytochrome P450 (CYP) responses, with negligible reproductive responses (Plotzke et al. 2000b; Domoradzki et al. 2017; WIL Research 1997a,b).

The organization of the document groups data according to organ- or system-specific effects. That is appropriate, but the structure does not relay an understanding about overall effects that might be synergistic or interactive. Additionally, the same studies are repeatedly reviewed because these datasets are large two-generation studies, which are often conducted by the same group of investigators. Thus, studies utilized for determining adverse effects, POD, and ascertaining effects are limited in number. Further, there are more recent studies that bring additional clarity to the D4 mechanisms of action and that document observed outcomes.

An updated literature search is recommended. The *Draft Human Health Hazard Assessment for D4* says that the literature search underlying this review was conducted in 2019 (US EPA 2025f, 59). There are at least three recent studies that examine reproductive toxicity and should be included in the *Draft Risk Evaluation for D4* (see Long et al. 2022; Tran et al. 2021; and Hanssen et al. 2013). The 2013 Hanssen et al. study estimates the amount of D4 from dermal exposure. Most of the reproductive toxicity discussion is based primarily on studies of exposure through inhalation, primarily via nose cone, with few whole-body exposure study designs. This likely indicates that EPA is underestimating the risk by not also considering dermal exposure or exposure of wildlife from grooming (preening, grooming, or allogrooming).

Tables in Appendix A effectively presented the Agency's analysis and evidence integration of the hepatic/liver, respiratory, and reproductive endpoints. Research by Tran et al. (2021) in mice found neurodevelopmental toxicity following D4 exposure, further emphasizing the need for an updated literature review to more fully document the potential health effects of D4 exposure.

Comments on the Hazard Endpoints and Mode of Action

The use of female reproductive effects seems to be overall well justified in the *Draft Risk Evaluation for D4*. It is reasonable to select live litter size as it was the most sensitive and best fitting of the endpoints modeled from the study. However, comments related to the downstream nature of that endpoint, the biological plausibility and human relevance remain of critical importance.

However, the Agency rated liver toxicity studies as high quality and reproductive studies as medium overall quality. Liver endpoints *should* be considered for POD derivation. Many studies listed in the liver effects section showed significant increase in liver to body weight ratios for exposed males (hepatomegaly). However, this effect was not considered in risk determination. This effect seems to be independent of the reproductive toxicity used for POD determination.

Some considerations for mode of action for liver effects. Animal studies show a strong effect on the liver, mainly hepatomegaly. However, the cause of increased liver weights is not known, both hypertrophy and hyperplasia are possible. Solid evidence supports CYP2B1 and CYP2B2 induction as an upstream effect. Additionally, no D4-related liver injury was observed in either males or females excluding the possibility of cytotoxicity as an MOA. Taken together, this indicates activation of Constitutive Androstane Receptor (CAR) as a possible mechanism of action. Similarly, D4 has estrogen

receptor α (ERα) activity, which may contribute to hepatomegaly as well. The EPA should evaluate these mechanisms for D4, or at a minimum state explicitly whether they have been evaluated. While the *Draft Human Health Hazard Assessment for D4* states that liver toxicity is *indeterminant,* a specific analysis of the CAR mechanism of action should be explored and described in the *Draft Risk Evaluation for D4*. These details are important in the context of human health effects.

There is moderate evidence for both effects on female reproduction and respiratory function in animals. Human evidence for respiratory effects is indeterminate based on one study of short-term exposure, and no human studies are available for female reproductive effects. The weight of evidence is stronger for female reproductive effects based on effects on female reproductive organs, estrous cycle irregularities, and mechanistic evidence, including the suppression of the LH surge, indicating that female reproductive effects is an appropriate critical effect. The selected study is a high-quality 2 generational study with multiple reproductive effects. Decreased live litter size is an appropriate POD, given that it was the most sensitive endpoint among those evaluated in the WIL Research (2001) study after successful BMD modeling.

Controlled Good Laboratory Practice studies conducted with rodents describe decreases in the number of implantation sites, estrous cycle disruptions, decreased litter size, failure to ovulate, decreases in corpora lutea, as well as decreases in maternal body weight during gestation and lactation. Mechanistic results suggest that D4 is a weak endocrine competitor with 3H-estradiol binding to ERα; other endocrine effects have been studied (e.g., delays in both the LH surge and in ovulation; see Quinn et al. 2007). However, Andersen (2022) provides logic to suggest that reproductive and kidney effects are rodent specific. Other identified endpoints from controlled inhalation studies in rodents include respiratory irritation and liver effects. The *Draft Human Health Hazard Assessment for D4,* the *Draft Risk Evaluation for D4,* and related technical support documents would benefit from a scatter diagram that plots NOECs and LOECs to ascertain levels where adverse effects have been described.

Together, the body of evidence presented in the draft documents suggests D4 has reproductive effects, and the use of the WIL Research (2001) study from which to develop a POD seems reasonable and should be protective of other effects described in rodents, although the human relevance is questionable based on Andersen (2022) and some public comments. In rodents, the preovulatory LH surge is sensitive to suppression by dopaminergic agents and phenothiazine-like chemicals. This disruption leads to decreased uterine implantation sites, fewer pups born, and reduced live litter size (Quinn et al. 2007). Whereas the preovulatory LH surge in primates is triggered by ovarian estrogen positive feedback, there is potential for the LH surge to be negatively affected by exposure to D4 through actions on neuroendocrine systems that also regulate the gonadotropin releasing hormone (GnRH) surge in humans.

The International Programme on Chemical Safety IPCS/EPA framework (IPCS 2007), provides a structured, transparent approach to evaluate if the weight of evidence is sufficient to establish an MoA in animals and whether that MoA is plausible in humans.

The human relevance analysis is highly specific for the chemical-MOA-tissue-endpoint combination under analysis in any particular case: different tissues, different endpoints, or alternative MOAs for a

given chemical may result in different human relevance findings. Meek et al. (2003) is a helpful reference for human relevance analysis.

Public commentors including Dr. Dekant posit a flawed argument that reproductive effects in female rodents do not have relevance to humans. This is also the position in other publications (for example, Andersen 2022 and Franzen et al. 2017). The Andersen (2022) paper discusses this in detail and questions the relevance of rodent data for human risk assessment. This is an interesting conundrum because the rodent model is considered the cornerstone of fundamental endocrinology studies and model for mammalian reproductive biology. More specifically, the argument in the Andersen (2022) publication is that the pre-ovulatory GnRH surge in rodents is modulated by GABAergic (gamma-aminobutyric acid, GABA) and dopaminergic (DA) neural systems resulting in LH release and stimulation of ovulation and that this circuit is disrupted by D4. Conversely, they argue that this differs from the ovulation inducing circuit in the primate/human, so the rodent data are irrelevant for risk assessment for human reproductive effects from D4 exposure. This argument is flawed for several reasons. First, there is evidence that other neuroendocrine elements, including hypothalamic kisspeptin neurons may coordinate the pre-ovulatory GnRH surge in both rodents and primates (Matsuda et al. 2019; Tsukamura 2022; Anderson and Millar 2022). Therefore, the argument that there are differences in human reproductive physiology compared with rats is correct according to the available data, but not entirely relevant, as these are conserved mechanisms across mammalian species that involve more complex coordinating neuroendocrine elements that produce similar MOAs for ovulation and the potential for D4 effects on these systems. Finally, studies using ethinyl estradiol or phenobarbital (PB) are not really totally representative; ethinyl estradiol is a potent estrogen with many other effects, including toxicity. PB is aligned with anesthetic-like specific effects that are interesting but may not be representative of a primary MOA.

As it stands, the current document suggests there is evidence of detrimental effects of D4 on the reproductive and respiratory systems in rodents. However, the determination of this POD was solely based on the two-generation WIL Research (2001) study. While it is a high-quality study that evaluates a wide range of doses and sensitive reproductive endpoints, it is questionable to utilize a single study for this determination as it *could* be underestimating risk. Further, the LOAEL of this study was 502 ppm, whereas the LOAEL in the Meeks et al. (2022) study was 301 ppm, which also showed significant reproductive effects (see EPA 2025f, Table 4-3). However, the Meeks et al. (2002) study does not seem to be included in the BMD modeling. Therefore, this more sensitive study is not considered in POD derivation. The EPA should run BMD modeling with the data from Meeks et al. (2022), as it showed significant effects at a lower exposure level. In addition, literature since 2019 that was not included should be considered. Finally, it is important to note that many of the studies referenced or included were conducted or sponsored by Dow Corning Chemicals. Having a body of literature that is so heavily weighted toward industry funding, with no independent or government studies, presents a potential conflict of interest and a potential source of bias.

Comments on the Systematic Review and Rationale and Selection of Hazard Endpoints

The Agency has conducted a thorough systematic review of the evidence and has done a good job of following the methods from their protocol to identify and assess human health hazard data. This

includes summary judgements and integrations by health outcome. When utilizing the underlying data as part of the systematic review for the risk evaluation, however, additional rationale and clarifications are warranted both regarding the selection of the WIL Research (2001) study as the key study as well as the specific endpoint selected from this study as the candidate POD for use in the risk evaluation. It seems that EPA has conducted the work to support these decisions but could do a better job substantiating them by using the data from the underlying systematic review.

- Section 4.1 provides a description of the data by outcome, including the apical data and mechanistic and supporting evidence, as well as the integrated summary. The *Draft Human Health Hazard Assessment for D4* does not, however, clearly discuss the selection of the WIL Research study as the key study, as was suggested by the opening statement of Section 4.2.1. EPA should provide this rationale.
    - Section 5.2 of the *Draft Risk Evaluation for D4* discusses the study selection (US EPA 2025h, 166). In this section, EPA identifies multiple factors supporting their selection of the study, including high overall quality and including a wide range of doses as well as a comprehensive set of sensitive reproductive endpoints across parents (F0 and F1) and offspring (F1 and F2).

From a methodological perspective, the EPA has followed their systematic review protocol and appropriately integrated the consideration of study quality (i.e., best available science) in determining key study selection. It is important to note that the Committee has previously commented on the limitations of the systematic review protocol and has offered recommendations for improvements that have yet to be implemented (SACC 2022).

- It is recommended that because multiple studies were categorized as “high” quality for consideration in dose response analyses in the systematic review, additional rationale be provided as to why the other “high” studies were not selected.

The paragraph referenced above begins with a description of NOAEC and LOAEC ranges across “most” reproductive effects; it would be helpful if this discussion were expanded such that the issue of selecting a study representing the most sensitive effects was also included. In doing so, it is recognized that BMD modeling benchmarks are difficult to directly compare to NOAEC and LOAEC values; thus, a qualitative discussion may be most appropriate. Additionally, spatial comparison (e.g., via a scatter diagram) of the $BMDL_5$ with other NOAECs and LOAECs should help provide a clearer view of the utility of the POD.

It is also of note that the *Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for Octamethylcyclotetrasiloxane (D4)* indicates that only studies that “reported HED derived from POD that contained lowest observed effect levels (LOEL) greater than an order of magnitude of the lowest HED LOAEL across existing assessments” were included (US EPA 2025a, 2). This is a little hard to follow; EPA should identify (as part of its rationale for selection of the WIL study) the studies excluded based on LOELs and list these LOELs in a diagram as the SACC has suggested for other aspects of this *Draft Risk Evaluation for D4*.

Recommendations

- Consider newer literature with additional measures that may provide a more sensitive indicator of adverse reproductive effects at lower exposure levels.
- Determine whether the additional MOA evidence impacts the rodent-specific "litter-size endpoint" as the basis for deriving a human health POD, given the significant mechanistic differences. Additional responsive endpoints could provide excellent basic information for establishing the most accurate POD.
- Evaluate the provided mechanistic data (Quinn et al. 2007; McKim et al. 2001; Andersen 2022; Plant 2012; Goodman et al. 2022) within the IPCS/EPA Human Relevance Framework to reach a conclusion on the applicability of these specific rodent reproductive endpoints for human risk assessment. The goal is to ensure that the final assessment is scientifically sound and relevant to protecting human health. Please refer to the discussion above in making this evaluation.
- Re-consider the hepatic effects and influence of the CAR mechanism, especially for males.
- Conduct BMD modeling with the Meeks et al. 2022 study data and consider and integrate that modeling into the D4 technical support documents and Draft Risk Evaluation. The Agency should represent the potential points of departure relative to general endpoint (e.g., organ system) on a scatter diagram of LOAELs/LOECs and NOAELs/NOECs and BMDLs to show that a body of information was used to select the POD, not a single study. For the selected POD, the Agency should also provide the $BMDL_5$ and ± 1 standard deviation (SD) estimates for clarity.

Additional Comments

Some Committee members disagree with concerns expressed by other SACC members that industry funded studies have the potential for bias. The point is that each study should be judged on merit of the design, conduct, and reporting, as the EPA has done in applying systematic review methodology and critical appraisal techniques. This is also noted in the Committee Response to Charge Question 2c. However, there are some concerns raised regarding the sensitivity of the WIL Research study and whether this study reports the most sensitive effects.

Editorial Comments on the *Draft Human Health Hazard Assessment for D4*

In Section 3.1.1 (human data), information about age and gender should be included.

On page 20, lines 684–685: Was endogenous D4 measured in the placebo? This need to evaluate D4 points to the error in omitting exposure from consumer personal care, cosmetics, food, and medicines.

On page 92, regarding the lengthening estrous cycles with some tests done in senescent females for long treatment times, lengthening estrous cycles is a feature of early aging and not senescence. Senescence means lack of cycles not the acyclicity associated with aging and cessation of ovarian function.

Section 4.2.1 begin with the following self-reference:

> As described in Section 4.2.1, EPA identified reproductive endpoints reported in the 2-generation inhalation study (WIL Research, 2001a) as the primary basis for the quantitative dose-response analysis.

This phrasing is curious, as it is in fact the opening statement of Section 4.2.1. The language should be clarified or corrected.

Selection of hazard endpoints and studies is the conclusion of the hazard identification step of the risk assessment process. The next step of the process is the dose-response analysis, including POD derivation. The related discussion in the *Draft Human Health Hazard Assessment for D4* is clearly presented. In Section 4.2.2 of the document, the Agency presents a number of considerations involved in selecting studies and endpoints. From perspective of one SACC member, two of these considerations are not appropriate at this stage of the assessment: (1) Total uncertainty factors; and (2) uncertainty and sensitivity of benchmark response (BMR) selection from BMD modeling. Considerations for selecting studies and endpoints should be focused on quality, including overall study quality and adequacy of the resulting data to support the dose-response modeling that will follow. The determination of the total uncertainty factor to inform the benchmark MOE relies on many of the same study and data quality considerations but is better placed as part of the dose-response analysis. Similarly, the uncertainty and sensitivity of BMR selection as part of the BMD modeling is an aspect of the dose-response analysis.

Charge Question 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 concentrations. 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.

Response

Aerosol Formation

The physical chemistry of D4 dictates that the exposure is most likely through inhalation, and the question becomes how the D4 aerosol is formed and the environmental conditions required to achieve the D4 containing vapor.

The studies primarily use inhalation exposure, with treatments using whole body exposure in a chamber (Meeks et al. 2022) or an appropriate dosage administered, usually through a nose cone.

Studies have tracked passage of radioactive D4 following administration; however, these studies reflect both D4 and transformed/metabolized forms.

Liquid aerosols can be formed in several ways, but the predominant process in a D4 workplace is probably by the condensation of a vapor into liquid aerosols or droplets. Usually this process requires

nuclei, preexisting liquid microdroplets or solids around which the condensation can occur. Nuclei are almost always present in the air, especially workplace air. The process is facilitated by the initial temperature of the liquid forming the vapor and the temperature of the air. A hotter liquid will produce more vapor. A cooler workplace atmosphere will cause more aerosols through condensation.

In short, aerosol formation is a complex process, depending on the characteristics of the material, the nature of the process that creates the aerosol, ventilation, the temperature and surface area of the initial liquid, air temperature, the amount of nuclei present in the air, and other factors. It is very difficult to model. Also, most aerosols are invisible.

The Krieger et al. (2021) study concluded that aerosol production occurred at 300, 500, 700 ppm D4 vapor concentrations during toxicity testing, but aerosol was not detected at lower vapor concentrations as confirmed by the inhalation expert Dr. Jürgen Pauluhn (Pauluhn 2021).

Measurement Challenges

The only way to determine the concentration of an aerosol is to measure it. Vapor and aerosol samples are normally collected by different methods: vapors by sorbent tubes, aerosols by gravimetric filters. Measuring both at once in a worker's breathing zone would require the worker to wear two sampling pumps, with two different sampling trains, or to have a single sampler that can discriminate between vapor and gaseous analytes. It is doubtful whether this has ever been done for D4.

EPA's limited D4 data are for vapor. There is no way to determine aerosol concentrations from those data. EPA made good use of the available data, but its limitations must be acknowledged. Of course, adding data on aerosols could never decrease, and would often increase, the measured D4 concentration in the air, and thus would increase inhalation and dermal exposures.

Toxicity Studies

The EPA cites a two-generation inhalation reproductive study in Sprague-Dawley rats (WIL 2001) for the outcomes for acute and chronic hazard identification and dose-response determination used to determine a POD.

Meeks et al. (2022) compared and found strain and gender differences in the responses of male and female Sprague-Dawley and Fisher 344 adult rats and phenobarbital-sodium salt was used for a control (IP 80mg/kg bw/day). Animals were subjected to whole body exposure in an inhalation chamber, and this publication provides an elegant explanation of delivery of a specific concentration in a chamber, which required heating to produce the vapor. Accordingly, the specifics of experimental design, including gender and animal strain, could introduce additional variability and overestimate the effective dose.

Exposure Scenarios

Vapor exposure would produce small gas molecules that would diffuse into the bloodstream via the lungs. For aerosols, the particle size would influence where it is deposited in the lung (upper versus lower respiratory tract). D4 has a moderately high vapor pressure, so it stays in the gas phase fairly easily. Aerosols may form when there is a rapid cooling or mixing that forces condensation or when close to saturation, which might occur during a very high emission incident like an industrial spill. Other

literature has shown that aerosols form at certain high temperatures, as well. EPA has identified one COU that might cause aerosol forming (application/use of paints and coatings). Without information describing particle size, it is difficult to make further hypotheses about how this may impact pulmonary toxicity. Given the known facts, it is appropriate that EPA focused on toxicity from vapor exposures.

Since it is known that at least some of the COUs generate aerosols, the Agency could consider aerosols and vapor as two independent exposure scenarios in the inhalation exposure studies. It is also important to determine which exposure scenario, aerosol or vapor, is more toxic. Even though vapors and aerosols are likely to co-occur and both will contribute to exposure, not having this information increases uncertainty and decreases the strength of discerning potential health risk. This information is important for D4 because the current non-cancer HECs and HEDs are determined using a two-generation inhalation exposure study.

Regarding D4 COUs generating aerosols, "At the highest exposure level, 20% of the test atmosphere was expected to be a liquid aerosol. The particle size was not measured." An accurate dose response and exposure concentrations will require particle size distribution to determine the percentage of aerosol particles with diameters < 5 μm.

It is appropriate that the Agency focuses on the D4 inhalation toxicity studies using vapor exposure at lower concentrations to assess human exposure to D4.

When considering whether vapor exposure or aerosol exposure of D4 is more potent in terms of toxic effects, it is important to consider that, in any given COU, it is likely that both occur at the same time, and it would be important to consider whether the relative contribution of one versus the other has an effect on toxic endpoints.

Data Gaps and Uncertainties

There is inherent uncertainty regarding the hazards associated with D4 aerosol exposure given the lack of epidemiology studies. However, a 2022 review of D4 modes of action includes a description of vapor exposure (Anderson, 2022).

Beyond potential aerosol exposure in the workplace, aerosol exposure is likely also occurring in homes via PCPs (e.g., releases from those that are scented). EPA should additionally consider PCPs as a route of aerosol exposure. In addition, EPA should consider environmental studies that measure D4 concentrations in different settings, which could be used to extrapolate exposure. For example, a 2013 study by Yucuis et al. measured D4 concentrations in indoor and outdoor air in Chicago and may provide information relevant to EPA regarding inhalation exposures.

A major limitation of the *Draft Risk Evaluation for D4* is that only workplace aerosol exposure is considered. While this is a major source and should not be disregarded, it is very likely that people are exposed to D4 in their homes, as well. D4 is present in PCPs, including both hair and skin care products (SCCS 2010), which further suggest dermal is another route of exposure. In addition, D4 is used in food packaging and breast implants, which are not considered in TSCA's purview. However, together these significantly contribute to human exposure.

D4 releases from the land or groundwater pathways are given insufficient consideration. As part of aggregate D4 exposures, D4 releases should be given more than cursory evaluation. There are numerous communities near municipal landfills and wastewater treatment facilities (with biosolids) where D4 is likely to be released. Also, on p. 9 Line 282 in the *Draft Environmental Media and General Population Exposure for Octamethylcyclotetrasiloxane (D4)*, there is a mention of fenceline community evaluation being conducted using draft guidance for which the SACC has provided comments (US EPA 2022). It is clear that EPA has not included many of the SACC recommendations for fenceline community assessments. The EPA should clearly state which SACC recommendations for improving the Fenceline Community Assessment Process draft were incorporated into the *Draft Risk Evaluation for D4* and which aspects of the Fenceline Assessment were not revised to include SACC recommendations.

Recommendations

- More recent literature should be incorporated to reduce uncertainty and select measures responsive to exposure scenarios (see Anderson 2022).
- Incorporate more recent detailed data that describe environmental aerosol concentrations in industrial settings, including air exchange, persistence in the environment, seasonal changes for heat related volatility of D4, and protective clothing for workers.
- measure or at least model the particle size distribution of Octamethylcyclotetrasiloxane (D4).
- Review the Supplemental Submissions from the American Chemistry Council to better understand the formation of aerosols in the breathing zone of animals during inhalation studies versus human exposure.
- Consider inhalation exposures from consumer products and other reasonably anticipated significant D4 sources.

Charge Question 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.

Response

The SACC generally offered no particularly substantive comments on the specific application of the BMD software; use of the BMD guidance and the model selection was generally supported. There were comments, however, that relate to dose-response modeling and thus overlap with responses to other charge questions with regard to: (1) requests for additional details and/or documentation for the modeling; and (2) requests for a rationale for the limited number of studies modeled.

Regarding the selected study and selected BMR, several SACC members commented that the EPA's dose response analysis and BMR selection seems appropriate for the outcomes. The reproductive endpoints that serve as the primary basis for quantitative dose-response analysis were mean litter size, mean number of pups born, and fertility from the evidence in a two-generation inhalation study (WIL Research 2001). These measures were reliable at exposure level of 700 ppm. Strengths included that the

benchmark response of 5 percent for reproductive endpoints has precedent and is appropriate for the severity of decrease in live litters. Also, the chosen model has an adequate fit and has the lowest Akaike information criterion (AIC), which is in line with EPA's Benchmark Guidance for selection of fit models. It was noted, however, that it would be helpful to clarify if the F2 offspring are directly treated or is it from maternal exposure), as this was the endpoint was used to establish the external HECs and HEDs via the PBPK model. It was also noted that the explanation of the relative deviation selection is outside of the BMD guidance; it is unclear why the Agency has used the definitions provided versus 1 SD. Providing additional rationale for this selection and possible deviation seems warranted.

Regarding biological relevance in humans of the $BMDL_5$, two commenters offered technical details of the response in context of human relevance. Although well-conducted, the WIL Research (2001) study did have significant variation in response which, in part, explains the $BMDL_{05}$ was below the NOAEC for the study. Further, not all similar studies found the same results at the same exposure levels, and it is questionable how well effects in rodents can model human reproductive responses (Andersen 2002). The strengths include reproductive corroboration of results in rodent and some mechanistic information; however, D4-mediated effects on GnRH neurons to block/ delay GnRH surge (dopamine) may not be relevant to humans (Andersen 2022). This suggests that there is considerable uncertainty about how well the rodent model emulates human responses. There is also considerable variation within and between studies in female reproductive response. Since the PBPK model includes exposures from inhalation, dermal, and oral exposures, there is significant uncertainty regarding the applicability of dermal exposures (for a volatile) and the variation in skin thickness (that affects penetration) and the timing and dose of D4 exposures for all three routes.

Additionally, the Anderson (2022) paper raises an interesting question. Basically, it questions the relevance of rodent data for human risk assessment. It's an interesting conundrum because GnRH is a key target (via GABA and DA neural systems impacts) resulting in reduced ovarian stimulation by LH and reduced ovulation. However, there are no data about direct links of this reduction in GnRH to reduced implantation and reduced live births, suggesting this is a system effect; meaning GnRH, LH, ovarian response, and implantation are all part of the circuit affected. Therefore, the argument that humans are different from rats is correct according to the data, but not entirely relevant as these are conserved mechanisms. For example, the argument of DA agonist/antagonist acting on prolactin (PRL) which is part of inducing the LH surge is correct. However, although primate/human LH surge is primarily dependent on ovarian produced estradiol positive feedback to the hypothalamic GnRH neurons and to the pituitary gland LH producing neurons, there is not a total separation in the MOA. Specifically, rats use both estradiol and PRL, whereas primates use estradiol primarily with corticosterone and PRL also involved. Finally, studies using ethinyl estradiol or phenobarbital (PB) are not really totally representative; ethinyl estradiol is a potent estrogen with lots of other effects including toxicity, PB is aligned with anesthetic-like specific effects that are interesting but may not be representative of a primary MOA.

The SACC also offered a number of comments regarding the completeness of reporting on the dose response modeling. Text from Appendix B reads, "For both males and females, fertility was measured in two ways—by an EPA method and an OECD method." However, the differences between the two measurements were not clearly explained. Further, what does the decision to use the former method

mean for the risk assessment and dose response analysis? The equation converting ppm to mg/m^3 is appropriate for 77 degrees (25 C); is there reason to believe this is the most appropriate temperature to use for the scenarios? If not, a different temperature should be used in the equation.

Regarding selection of the WIL Research (2001) study and modeling of other studies (noting that these build on comments offered in charge question 2a), multiple SACC members echoed concerns about the limitations of a single study approach, particularly when the EPA has so much more data available via systematic reviews. Thus, comments were offered in support from those in charge question 2a that dose response arrays and/or additional modeling would be informative. Several SACC members noted support for combined data analyses and probabilistic techniques be considered to more fully ensure the health-based PODs represent the evidence base. Using such techniques is in line with the recognized desire for more advanced modeling, and, given that the Agency is required to use the best available science, Bayesian, model averaging, etc. *are* the best available science and we are not using them. It is not clear whether the updated BMD software that contains these functionalities are available to TSCA and were not used, or whether they are not yet available. It would be helpful to have that clarified.

Regarding the WIL Research (2001) study itself, several commenters expressed concern regarding conflict of interest: All four studies come from industry (Dow Corning, Pfizer) and focus only on the rat. This concern is not shared by all SACC members, as science should be judged based on design, conduct, and reporting via the systematic review, which the EPA has done.

Regarding consideration of other studies, many members commented on such. It is recommended that EPA address and provide rationale for the following issues:

- The dermal exposure study IRDC 1993c was not considered for dose response analysis but was given an overall quality determination of “high.” This seems contradictory.
- Several well-conducted studies in rodents show dose-response relationships of D4 affecting aspects of female reproduction.
- Not selecting liver endpoints, especially in males, for BMR should be further justified. There are some issues related to using the current uncertainty factors, which do not seem to be entirely justified. This is critical because HECs are determined using PBPK modeling, which does seem to consider uncertainties. This also applies to PESS. There is no consideration for presence of significant obesity in the American population. Approximately 40 percent of Americans are either overweight or obese. This is especially critical for chemicals like D4, which are sequestered in the adipose tissue. Since PBPK modeling can take this into account, the Agency should conduct additional modeling with increased fat content to cover obese population.
- A public commenter commented that the dermal POD from Canada is 100 mg/kg/d from European Commission is 17.8 mg/kg/d, which are more than three times lower than EPA estimates of 326 mg/kg/d. The EPA should explain why there are differences. Specifically, EPA should explain the appropriateness of their selection for Area Under the Concentration-Time Curve. Of note, this commenter also indicated that AUC is not defined anywhere in the *Draft Risk Evaluation for D4*.

With respect to the application of the modeling, it was noted that HECs and HEDs used to calculate risks are applied to all age groups and include D4 COUs, including acute, intermediate, and chronic. The lack of distinguishing these life stages, lengths of exposure, and source of exposure (industrial, PESS, environmental) introduces additional variability that underestimates risk.

The SACC also recognizes that three public commenters addressed the dose-response and DMR selection. Based on such, it is recommended that the EPA consider adding rationale as it relates to clarifying the reliance of the 2012 BMD guidance for the selection of the BMR, portal of entry effects, and human relevance of the rodent reproductive endpoint.

The SACC offers two key recommendations with respect to dose-response modeling:

- EPA has done a traditional amount of research and assessment via systematic review. Thus, EPA has the information to add rationale for the limited number of studies modeled. We recommend EPA better translate the information from the systematic review in context of the decision to select a single study or, preferably, EPA consider modeling additional studies and outcomes to ensure the PODs are sufficiently protective.
- Additional details and/or documentation for the modeling and rationale for BMR selection be provided.

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.

Response

The SACC offers the following comments regarding the Agency's chosen values from 2020 CDR production volume data as the basis for both screening and refined assessments.

First, the rationale for selecting 500 million pounds per year as the upper-bound production volume is not sufficiently explained or justified. The *Draft Risk Evaluation for D4* provides only a brief description of the production volume determination, and key elements of the data evaluation process remain unclear. For example, no information is provided to describe the number of reporting facilities; the number of facilities claiming CBI; number of facilities that may produce or use D4 but are not required to report; or whether reported values exclude confidential business information (CBI)-claimed production. This limited transparency makes it difficult to evaluate whether 500 million pounds per year is a scientifically defensible upper-bound estimate for screening purposes. The SACC has previously advised EPA that, in

the absence of verifiable data, high-end production estimates and release values should be used. The information currently provided in the *Draft Risk Evaluation for D4* does not convince the SACC that 500 million pounds per year is indeed a high-end estimate. Excluding CBI-claimed production data from non-reporting facilities may well underestimate production volumes. These omissions would also bias release results downward. In the absence of more complete reporting from the trade organization [Silicones Environmental, Health, and Safety Center (SEHSC)] petitioning for this review, EPA should include high-end estimates for missing values, consistent with previous SACC guidance, to avoid underestimating potential exposures and releases.

Second, given that this risk evaluation was specifically requested by the SEHSC, EPA should obtain clarifying information from SEHSC regarding production volumes from this entity and its constituents. At a minimum, this information could be used to evaluate the appropriateness of the selected upper bound value.

Third, EPA must justify why 2020 CDR values are considered most representative of current conditions, particularly because 2020 values (which include reporting years 2016–2019) are lower than earlier cycles. While using the most recent data may be reasonable, the draft does not explain why production appears to have declined or how historical trends informed EPA's selection of the 500 million pounds per year value. The 2020 CDR data was presumably reported in 2020 and 2021, so the added stresses of COVID-19 would have impacted accurate reporting. We recommend additional clarity in Section 2.3.1 to describe how historical information was evaluated. If the 2024 CDR data are finalized in time, EPA should consider incorporating these more current data into the *Draft Risk Evaluation for D4*, although we acknowledge that the 2024 data (which would include 2020–2023) likely could not be representative given the COVID-19 impacts to industry and production volumes during this time period.

Fourth, there are inconsistencies in the terminology used to describe the production volume applied in refined assessments. The documents refer to 375 million pounds per year as both a "mean" and a "midpoint." EPA should clearly state whether this value is a median, arithmetic mean, or geometric mean, describe why that statistic is appropriate for the underlying data distribution, and apply the term consistently throughout these documents.

Fifth, reviewers noted the need for clarity regarding the types of releases included in the assessment. Because the analysis focuses on occupational exposure scenarios, releases that fall outside occupational settings appear to be excluded. EPA should clearly state these limitations and discuss how non-occupational releases are addressed or why they are not evaluated.

After EPA estimated production volume, they constructed COUs and OESs. In this and past risk evaluations, the Agency did this without visiting a single manufacturing or production facility or observing a single work process. This makes it difficult to reliably evaluate sampling data, to separate directly exposed workers from ONUs, or even to understand how discharges to air, water, or soil occur. The OCSPP staff are not to blame for this; the decisions were made at a higher level and were understandable given EPA's budget constraints. Visits to manufacturing and production facilities would improve future risk evaluations. OSHA requires that private sampling data be made available to them, an interagency agreement between OSHA and EPA could be explored as a means to get more data.

Recommendations

- EPA should include high-end estimates for missing values, consistent with previous SACC guidance, to avoid underestimating potential exposures and releases.
- EPA should obtain clarifying information from SEHSC regarding production volumes from this entity and its constituents.
- EPA should clearly state which types of D4 releases were excluded from this assessment and discuss how non-occupational releases are addressed or why they are not evaluated.
- Obtain industrial compliance sampling data from OSHA and SCHSC. Perhaps an interagency agreement between OSHA and EPA could be explored as a means to accomplish this.

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 approach 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.

Response

The key concern with the approach used by EPA relates to data limitations. Industry has not provided basic information needed to improve release estimates, leaving EPA to rely almost entirely on highly variable PV data. Reported PVs vary dramatically (e.g., the 2020 PV is half the 2016 value with no explanation, though one Committee member thought this could be due to less demand from Europe/internationally and a decreased global demand), making this a weak basis for modeling. Experts The public commenters, Arnot and Dekant, indicated that better data may exist, and the SACC has asked them and SEHSC to provide those data. In the absence of improved data, EPA is justified in using upper-end PV values. Historical data suggest that 500 million pounds may represent a typical level rather than an extreme one. In the absence of actual D4 production volume data, a value higher than 500 million

pounds is likely to be needed to proceed with a risk evaluation that protects humans and ecological receptors.

The *Draft Environmental Release and Occupational Exposure Assessment for D4,* Section 2.3.3, details using mean values from an OES for non-reporting facilities. This is inappropriate. Facilities that do not report use or release must be assumed to release a high centile, perhaps the maximum amount from within their respective OES. If refinement of that approach is needed, use or release data must be obtained from the non-reporting facilities. Obtaining these data from non-reporting facilities would also allow refinement of estimated daily release amounts and release frequencies.

The *Draft Environmental Release and Occupational Exposure Assessment for D4* does not specify how many facilities fall into each rung of the hierarchy, or how much reported data is being used as compared to estimations, which would be helpful for being able to evaluate the overall uncertainty. Or, if all data were estimated, a comparison of how the model estimated known values (based on facility report) would be helpful to instill confidence in the model. The EPA should include the number of facilities that reported their total annual release rate information but did not provide release frequency information or other metrics. If these descriptions are reported elsewhere, they should be referenced in Section 2.3.3.

The SACC has concerns with model assumptions and defaults. EPA's current modeling framework appears to assume a single facility contributing to environmental load. However, multiple facilities often cluster geographically and discharge to shared air or water bodies. Under such conditions, even moderate releases from multiple sources could combine to produce unacceptable exposures. EPA should therefore consider probabilistic methods—such as Monte Carlo simulations incorporating full release-day and annual-release distributions—to evaluate the likelihood that simultaneous releases from two or more facilities could create high daily loads. Many of these approaches are provided in the EPA's *Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities* (US EPA 2022) and the SACC's Peer Review of that approach to fenceline assessments (US EPA 2022).

Clarification of modeling intent is also needed. It is unclear whether the calculated release volumes and release-day estimates are intended strictly for screening-level evaluation or are being treated as representative, normalized exposure inputs for a refined exposure assessment. This distinction is critical, as parameter selection, default assumptions, and interpretation of results should differ substantially depending on intent. EPA should clearly state the purpose of these calculations and ensure that the modeling approach and parameter choices consistently align with that stated purpose. Given the magnitude of uncertainty associated with the available production volume and release data, conservative modeling choices—including values that predict upper bound exposures—are appropriate and justified until more precise, facility-specific information is provided by industry. Key determinants of cumulative risk include differences in release distributions across facilities, the number of days each facility releases, and the number of facilities within a shared environmental catchment. Even if individual facilities release at median (50th percentile) levels, combined daily contributions from several neighboring facilities may exceed acceptable thresholds.

From a risk perspective, the relevant question is the probability that cumulative contributions from multiple facilities on a given day combine to exceed an unacceptable load, even when individual facilities

release at moderate levels. If this probability is non-trivial, then concern is warranted regardless of whether any single facility dominates the release profile. EPA should explicitly frame and evaluate this probability within its modeling approach.

The log normal distribution is typically assumed for chemical concentrations in an environmental medium. Often there will be fewer very high concentrations (only very close to a spill, for example) and as the chemical disperses in the environmental medium, concentrations become diluted so there are more values at the central tendency and lower concentrations (but still bounded by 0 on the lower end). This seems to be analogous to what is being described for release days. It is unclear whether release days would follow a log normal distribution. The various COUs could represent quite different D4 use patterns (e.g., continuous or cyclical). It would be helpful to have some corroborating data to help support the resulting distribution.

While there is an overreliance on default assumptions, the reasoning for these default assumptions is not adequately described. For example, 350 days for commodity chemicals is tied to 50 weeks of operation/2 weeks of turnaround, but there should be assumed variability in turnaround scheduling. Positing 250 operational days for low-volume specialty chemicals assumes no weekend production, which is likely not true for many specialty chemical manufacturers. Default day counts should be informed by data from relevant industry sectors, not general assumptions about weekly schedules. Without justification, high-end estimates should be used.

Overall, the method that EPA has landed on seems quite complicated and could be simplified by using data for production volumes on days a facility is in operation, which EPA states is unknown. This uncertainty is unacceptable, and these data must be obtained from the manufacturers or producers to perform any type of scientifically credible risk assessment. Using total annual release and dividing by the average daily release to obtain days of release is likely masking the potential high end of the release distribution. In the absence of more reliable data, EPA should use a lower bound (or centile) of production days and an upper bound (or centile) of production volumes to estimate daily release. If EPA sticks with the method presented in the draft document, then central tendency rather than high end should be used to maintain some modicum of certainty that models are not predicting released that are far lower than actual.

In particular, reliance on high-end releases from a single facility or COU may not be the most health-protective approach when multiple facilities contribute to a shared environmental medium. Lower per-facility releases (e.g., central tendency or median values) occurring across many days and from multiple nearby facilities may, in combination, yield a higher cumulative daily load than a single high-end release assumed to occur infrequently. EPA should explicitly evaluate this tradeoff and ensure that the selected approach does not underestimate cumulative exposure potential in multi-source scenarios.

EPA should more fully address disposal pathways, particularly for communities with marginal waste containment scenarios. These include rural, Arctic, and Tribal communities, especially those with permafrost conditions, open-pit disposal practices, or limited engineered containment. Such disposal conditions can result in direct and ongoing exposure to the general community. These scenarios are particularly relevant to PESS, which EPA is required to consider under TSCA.SACC recognizes the

challenges in assigning contaminant mass to specific disposal-related OESs and media. Even so, better characterization of disposal, recycling, and repurposing pathways warrant additional effort. EPA's Office of Chemical Safety and Pollution Prevention has previously outlined relevant considerations and approaches in its September 2024 guidance, which should be explicitly incorporated into this assessment (US EPA, 2024).

Recommendations

- Acquire more complete and appropriate industry data. Data underlying this analysis are poor. Given that industry requested this review, the petitioning trade group should be required to provide the needed data. EPA should require industry partners to share the data needed to improve this and any future RE.

In the meantime, EPA should:

- Treat upper-bound PV values as justified defaults (given lack of industry data to assume otherwise) and highlight the large drop in PV reporting from previous years and the unexplained uncertainty that presents extend Monte Carlo modeling to evaluate cumulative emissions from multiple nearby sources.
- Rely on distributions showing high frequencies of release days when assessing realistic daily load contributions.
- Consider evaluating two or three common facilities to determine what is the probability that they would exceed high exposure load on any given day. Looking at these facilities in depth could help to confirm some of the assumptions made by EPA.
- In the absence of more reliable production data, use a lower bound (or centile) of production days and an upper bound (or centile) of production volumes to estimate daily releases.

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. For the sediment samples from DD1 and DD4, the concentrations were flagged as estimated because the concentrations for most of the samples were reported above the highest laboratory standard used to construct the calibration curve. The surface water samples at ECA DD1 and DD4 were primarily below the limit of quantitation (LOQ) while the estimated D4 sediment concentration were two orders of magnitude greater. Sediment and surface water sample concentrations can be found in the ECA Report volume 1, Table 3-1 on page 180, and Table 3-4 page 184 for DD4. Observation of low surface water D4 concentration over elevated sediment D4 concentration is not apparent in other modeled or monitored OES. 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.

Response

The Committee reviewed sediment monitoring data for D4 and identified several issues related to analytical uncertainty, calibration-range exceedances, and interpretation of environmental concentrations. The Committee recognized that sediment data provide meaningful evidence of environmental conditions but require better documentation and more transparent handling of uncertainty.

The Committee identified significant uncertainty in sediment samples that exceeded the validated upper calibration limits of the gas chromatography-mass spectrometry method. These exceedances created concerns about detector nonlinearity and low-biased quantitation, which could cause either overestimation or underestimation of actual concentrations, although underestimation is much more likely. The Committee recommends that EPA provide a clear statement identifying which samples fell outside the calibration range and a transparent explanation of how they were processed—whether estimated, extrapolated, or flagged for caution. The Agency should also include information for each sample matrix representing samples exceeding the calibration range as proportion of (1) detectable value; and (2) total samples. It is worth noting that E-flagged D4 results underwent data-usability review and were not rejected. Although dilution or other analytical adjustments should have been performed at the time for samples above the calibration limit, the Committee agreed that re-analysis of D4 in any given sample at this stage would require procedures that substantially deviate from the established standard operating procedure.

The Committee also noted inconsistencies in the reporting and explanation of method detection limit, method limit of quantitation, and reporting limit values. Tables included missing units, negative concentrations, and unclear conversions (for example, ECA Report Volume 1, Table 3-1, p. 180, and Table 3-4, p. 184, ERM, 2017). These issues reduced the clarity of the analytical data and interpretations and complicated efforts to trace how limits of detection and quantification were derived and applied across the dataset. In addition, the Committee believes it would be useful to justify the use of three times the method detection limit as the reporting limit or method limit of quantitation. If the method detection limit has been properly determined, it should serve as the quantitative limit for risk assessment. Using three times (3×) the method detection limit instead may artificially raise the quantification threshold for risk assessment. The EPA could evaluate alternative scenarios using the method detection limit, three times the method detection limit, and other potential reporting limits to determine whether differences in computed statistics are significant. If significant differences are observed with these different reporting limits, then the reporting limit is too high for the risk evaluation.

Despite these analytical concerns, the Committee recognized that the pattern of low D4 concentrations in surface water and elevated concentrations in sediment aligned with expected environmental behavior of D4 due to its strong hydrophobicity, volatility, and affinity for organic carbon. The pattern also suggested the possibility of multiple contributing sources, including sludge, landfill leachate, atmospheric deposition, and runoff, as well as the presence of a degradation product, DMSD. These factors indicated that elevated concentrations in sediment reflected plausible environmental conditions (e.g., organic carbon partitioning and sediment deposition/burial under potentially non–steady-state conditions) rather than solely analytical uncertainties.

The Committee further identified several implications for risk assessment. Hazard quotients often exceeded 1, and in some cases exceeded 3. These higher values required clear communication rather than aggregation into broad categories (such as exceeding 1) that obscured the degree of potential risk. Sediment datasets exhibited skewed distributions, which warranted the use of geometric means and upper confidence limits (UCLs) rather than simple arithmetic averages. The Committee also recommended separating analytical uncertainty from uncertainty inherent in exposure and risk estimation, ensuring that each source of uncertainty was clearly assessed.

The Committee highlighted several specific issues in the *Draft Risk Evaluation for D4.*

- Industrial sites can release D4 into wastewater treatment plants, surface water, air, and landfills (US EPA 2025h, 20). All sources must be considered and the deposition into the surface water and underlying sediment may also continuously occur with leaching from landfills (although later in the document EPA states that landfill leachate should not contain high concentrations of D4), sludge, and runoff events from soils that have pesticides and other chemicals potentially containing D4, as shown in Figure 1-7 of the *Draft Risk Evaluation for D4*.
- Given the difference and potential disconnect in the sediment versus the surface water D4, transformation products, bioactive metabolites should be considered. This is especially important given the persistence in sediments for D4 and its metabolites, specifically DMSD.
- The issue of D4 content in landfills merits further consideration, as home use products are likely to be discarded, and their breakdown may release D4 into the soil or air. Although deemed low risk, there are instances of release (see US EPA 2025h, 76–78, Table 3-9). DMSD is a terminal degradation product, persistent in the aqueous environment, with evidence of potential harm based on adverse population level effects that may be rather insensitive. As such, quantitative risk assessments must include the range of monitored samples, including those outside the calibration curve, as this will reflect the variability in exposure concentrations that wildlife may encounter.

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.

Response

The Committee agreed that the current assessment appropriately acknowledges uncertainty regarding the extent of D4 releases to water for 13 OESs representing 18 COUs. The Committee also agreed that the sensitivity analysis in Appendix J of the *Draft Risk Evaluation for D4* highlights the aquatic toxicity of D4. Additional accurate information is needed to better describe releases to surface water. EPA should provide spatial relationships for all releasing facilities, perhaps on a map. It will also be important to know whether facilities releasing D4 are proximate to wastewater treatment facilities that may be releasing additional D4. Please note that the highest D4 measured in outdoor air is 2.11 µg/m^3 near an aeration tank at a wastewater treatment facility and the second highest value was above a landfill (0.47 µg/m^3) as shown in the *Draft Physical Chemistry and Fate Assessment for D4* (US EPA 2025g). Thus, omitting wastewater treatment plants and landfills as sources of airborne D4 underestimates D4 exposures. This information is included here given EPA's reliance on wastewater treatment effluent as the major source of D4 release and EPA's reliance on wastewater treatment plants to remove D4 before release to surface water.

The Committee noted that reducing uncertainty (lack of knowledge) is achieved through data collection. A representative and refined analysis that reduces uncertainty requires an adequate data set, collected at a set of locations that reflect all D4 COUs. An assessment built with adequate data representative of D4 COUs would be health protective and would reduce uncertainty.

ECA Volume 1 documents (ERM, 2017) measured concentrations of D4 in influent, effluent, surface water, sediment, and biota at multiple wastewater treatment plants. Results showed that D4 concentrations in surface water were generally at or below the limit of quantitation (0.06 µg/L), while sediment concentrations were often much higher (up to 11,000 ng/g). The Committee noted that this confirmed that aqueous concentrations of D4 in surface waters are minor compared with those retained in sediments or removed via wastewater treatment, consistent with the finding that majority of D4 is removed by sorption and volatilization in wastewater treatment plants. Therefore, modeled "releases to water" in the *Draft Risk Evaluation for D4* may overstate realistic exposure, since the empirical monitoring indicates low D4 concentrations in surface water despite measurable sediment residues.

Some Committee members noted that in the absence of additional release information, the current assessment would benefit from additional refinement to ensure that modeled assumptions are both health-protective and representative of real-world conditions. A modeling approach would build on the available monitoring data with assumptions guided by established practices and D4's physicochemical

properties (e.g., volatility, hydrophobicity, and high removal efficiency in wastewater treatment). For example, rather than assume that 100 percent of releases go to water, another approach would be to assume that the maximum D4 that can dissolve in water is the maximum release to water. The current assessment shows some modeled concentrations that exceed D4's solubility, which is only physically realistic if the D4 (1) is sorbed to suspended solids; (2) has enhanced solubility from dissolved organic matter; or (3) is present as microdroplets. EPA could refine this by constraining model results with solubility limits or conducting probabilistic simulations that better reflect plausible distributions of media partitioning. Other modeling refinements could include probabilistic or tiered apportioning of releases to different media, constrained by D4's known physicochemical properties.

Total concentrations of D4 in the water column that are above water solubility limits would be caused by droplet or film formation and would facilitate sorption to sediments or suspended solids. These fractions could be modeled. It should be noted that the release of D4 in droplet or film form could explain the low concentrations in water (at mid depth or deeper) overlying heavily contaminated sediments, described in charge question 5.

Some Committee members recommended empirical cross-validation using available monitoring data (e.g., from the D4 Environmental Monitoring Final Report) ERM, 2017)to further strengthen confidence in modeled outcomes, and clearly presenting quantitative uncertainty bounds or sensitivity results for media-specific release fractions would enhance transparency and scientific defensibility of the risk evaluation.

Specific Committee comments follow.

- A farm pond scenario was included for water body modeling in the *Draft Environmental Media and General Population Exposure for D4* although the Point Source Calculator and flow metrics do not seem to be relevant to a farm pond model. (US EPA 2025d, 34)
- Upper bounds of concentrations in water could be corroborated through monitoring data, with the caveat that concentrations above the calibration range would need to be somehow adjusted for non-linearity or for organic carbon content in water.
- Evaluation of the actual calibration curves would be necessary (Appendix C.1.5 is on p. 10081, ERM, 2017)). In reviewing those calibration data (pp10370-10373), it was not apparent whether the values in question were above the maximum standard for the low or high calibration curves. Discerning any specific calibration detail in the report is difficult. For data above the calibration curve, the "error" could be estimated as the variance in calibration slope that was observed on the actual data of analysis, as long as the estimated value is not more than ~10–15 percent from the top of the calibration curve. For example, a line that had a slope of (±10 percent) would translate into a concentration that could be 10 percent higher than reported. Upper confidence bands for the regression could also be determined.
- Many Committee members noted that EPA did not include consumer use of D4 in PCPs and noted that use of those products influences discharges to water through down-the-drain disposal. These release scenarios are included only as components of discharges from wastewater treatment plants with small industrial inputs in the current assessment. Wastewater

treatment plants can be much smaller than those reported, as can receiving waters, and this breadth was not captured. There is also no evaluation of releases to septic systems or dissolution of D4 from consumer products into waterbodies. No assessment has been made of D4 volatilization from wastewater treatment plants or from septic systems.

- In the *Draft Environmental Media and General Population Exposure for D4*, aqueous exposures are modeled through the Point Source Calculator using water releases, and tracking those releases to the *Draft Environmental Release and Occupational Exposure* document leads to information that includes no releases from consumer products. Thus, the circular references in the assemblage of documents in this docket does not contain any assessment of general population exposure to D4 sources other than direct industrial releases from manufacturing or from wastewater treatment plants.
- The Canadian Government Risk Assessment of Decamethylcyclopentasiloxane (Siloxane D5); concluded that, during use, 9–10 percent of D5 in soaps and shampoos was rinsed down the drain (ECCC 2022). This type of release does not appear to be captured in the current risk assessment. This omission is perplexing given the statement in the *Draft Physical Chemistry and Fate Assessment for D4* that "the main sources of D4 are from wastewater effluents and down-the-drain disposals from industrial and consumer uses." (US EPA 2025g, 49)

Recommendations

- Obtain an adequate data set, collected at a set of locations that reflect all D4 COUs, to reduce uncertainty.
- Provide spatial relationships for known releasing facilities and consider exposures from multiple sources when they are sufficiently near to one another to allow significant D4 transport from one source to another.
- Consider empirical cross-validation of D4 concentrations in water using UCL_{95}s of available monitoring data (e.g., from the D4 Environmental Monitoring Final Report) (ERM, 2017) to strengthen confidence in modeled outcomes.
- Include D4 in PCPs in the release estimates.

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.

Charge Question 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 available field-measured BAF values 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.

General Comments

Estimating D4 exposures using conventional means (e.g., BAF) is not straightforward. Given that D4 is primarily lipid soluble with limited water solubility, exposure of aquatic organisms is likely a consequence of water fraction and adhered organic fractions (particulates), and a multitude of other factors in water. Studies have shown that a very small proportion of D4 is absorbed via the gastrointestinal (GI) tract in fish (<13 percent, Cantu et al. 2024). sing the non-diet BCF seems reasonable, yet there should be recognition of the variability that would be realistically expected. The Committee agrees with the comments from Dr. Gobas that the EPA should also use the output from various models and compare those values with those calculated from controlled laboratory studies and examples of various biota in freshwater and in marine environments where body burdens have been reported. These latter data could also be used to estimate exposure since a Trophic Magnification Factor (TMF) could not be demonstrated (e.g., Jia et al. 2015).

The use of BCF in lieu of BAF is consistent with the screening-level analysis conducted (as described in the *Draft Environmental Media and General Population Exposure for D4*). For a screening analysis it is appropriate to use inputs that reflect higher exposures (overestimates) with the understanding that, if the risk characterization indicates an increased risk, a refined analysis should be conducted. EPA should note that a BAF should never be lower than BCF because BAF integrates all routes of exposure (e.g. gill and oral), while the BCF includes only a subcomponent (e.g., only gill exposure). In this case, the conservative assumptions resulted in a higher BCF. This is covered in more detail in the next paragraph. A screening analysis is a health-protective approach using data that may overestimate exposure potential in situations where data availability is limited. It seems to have served this purpose for the screening level, as fish ingestion does not appear as a driver of unreasonable risk in the *Draft Risk Evaluation for D4.*

This charge question, focused on the validity of using BCF instead of BAF to calculate fish tissue concentration from water concentration, is somewhat moot. EPA showed that the maximum measured fish tissue concentration from the ECA study results in an MOE well above the 30 benchmark for all consumer and Tribal exposures to dietary fish. Therefore, there is no need to model uptake by fish based on estimated (or modeled) discharge water concentrations. That said, the logic of using BCF as an upper

limit of water-to-fish uptake is sound for this situation and with reference to the available data, if it is done using stable state values. As EPA noted, the dietary portion of total D4 uptake is known to be significantly less than that of the gill exposure and may not contribute significantly to the total body burden. Additionally, it is possible that the laboratory exposures force greater gill uptake than is seen in natural systems, as most of the studies are conducted with closed headspace, thereby reducing volatilization and increasing the water concentration. This would result in a conservative (i.e., higher) calculated BCF as compared to natural systems. However, BCF estimates that were made from dietary only exposures and then estimating water concentrations from which the BCF is calculated could produce lower than expected values due to biotransformation processes in the GI tract. These studies (see US EPA 2025c, 40–41) state that the BCF was derived from only the BCFss (ss = steady state) studies (water-only exposure), with no rationale for excluding studies. EPA should present their reasoning in the document.

As mentioned above, BAF should never be lower than BCF because BAF integrates diet, but BCF does not. However, in practice, a measured BAF can be lower than a BCF determined from well-designed experiments when field studies are small, not at steady state, or have diet composition uncertainties; that is, exactly what is observed in Wang et al. (2021) and Guo et al. (2021) for D4 (see US EPA 2025g, 43, Figure 3-5). Also, there is no "universal" BAF for D4, or any other chemical. The BAF varies with site-specific water versus dietary exposure. The difference between BCF and BAF can also become minimal if a chemical has a low dietary uptake efficiency and/or undergoes substantial intestinal or first-pass biotransformation.

Moreover, the above counterexamples do not justify replacing BAF with BCF; they simply highlight data-quality and design issues in the field BAFs and the need to analyze them with appropriate censoring/weighting rather than redefining the metric hierarchy. As Dr. Frank Gobas emphasizes in his public comment, BAF depends on the relative concentrations in water and diet, so if prey concentrations are high, diet can still dominate even with lower uptake efficiency or fast intestinal or first-pass biotransformation.

Technical Comments

The data/studies used for the BCF calculation are in the *Draft Environmental Exposure Assessment for D4* (US EPA 2025c, 24, Table 3-1). However, EPA used only a subset of the studies shown in Table 3-1, specifically those that are labeled as BCFss with water-only exposures. There were several other studies listed and qualified as high quality that exposed fish through food and back calculated the water concentration; apparently, these studies were not used in the final BCF calculations. All these studies are described in the *Draft Environmental Exposure Assessment for D4* (US EPA 2025c, 40–41), which states that the BCF was derived from the BCFss without explaining why the others were excluded. In addition, the Committee agrees that dietary exposure studies (to back calculate a water concentration) should not be used in the BCF determination; however, EPA should explain their reasoning. Finally, there is merit in considering the use of maximum field-measured or UCL_{95} D4 concentrations in fish tissue for BAF calculations, as these measurements could provide the most accurate scenario for outcomes from field exposures.

Specific Comments

The EPA considered the BCF dataset more robust. However, the biotransformation of D4 in fish GI tract diminishes the concentrations of D4 in fish tissue. The EPA should address the potential for metabolites to be bioactive. Metabolites, uptake, and effect models should consider these additional chemicals, or the EPA should discuss this additional source of uncertainty.

The conclusion that metabolism of D4 in the GI tract precludes significant accumulation from dietary exposures ignores the metabolites, which may also be bioactive (US EPA 2025c, 30) see studies described below). The D4 transformation products seem to be dismissed because studies are lacking or suggest less potent effects.

Domoradzki et al. 2017 tracked radioactive D4 and reported a high proportion of parent compound, D4 in tissues; however, liver showed more transformation products. EPA should explain the extent to which laboratory and field studies consider potential bioactive metabolites of D4 or bioindicators of activation of toxicant-related physiological responses (liver enzymes, etc.)? In addition, the radioactive tracking studies may not separate D4 from transformation/metabolized products.

A similar study in juvenile rainbow trout showed negligible transformation, except for liver and GI tract, which contained metabolites. Accordingly, it is important to evaluate transformation products that may occur in various media (water, sediment, etc.) as part of the overall model, as some of the disconnect may be due to an incomplete characterization of the parent and transformed/metabolized compounds.

Recommendations

- BCF should be used only in lieu of BAF when there is clear evidence that water-borne uptake is the main source of chemical uptake by in the fish of interest.
- If there is evidence for water-borne uptake as the primary source of uptake, then EPA should clearly state in the report the use of BCF instead of BAF as a practical choice, not a general principle.
- The most accurate estimate of D4 concentrations in fish tissue should be used in probabilistic exposure models for total daily exposures. However, consider a comparison of modeled (e.g., parametrized ADME-B), measured, and experimental data.
- Determine if D4 metabolites and transformed products in the environment are bioactive, and if so, the models should consider these additional chemicals in the models as an additional source of uncertainty.

Charge Question 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.

Charge Question 7b.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.

Response

The Committee commends EPA for its transparency in articulating the analytical challenges and sources of uncertainty in determining D4's bioaccumulation potential in the *Draft Physical Chemistry and Fate Assessment for D4* (see US EPA 2025g, 47, Section 3.6.6). The SACC also appreciates EPA's decision to exclude three studies that reported aqueous exposure doses exceeding D4's water solubility (See US EPA 2025g, 40. This is a defensible choice when determining BCFs because such tests likely fail to represent the dissolved, readily bioavailable fraction. The SACC also noticed that this exclusion narrows the usable dataset and increases the weight placed on the remaining studies.

The use of BCF reflects D4 uptake by aquatic organisms directly from contaminated water, generally via gills and not by diet. However, attempting to estimate BCF in laboratory studies excluded three studies due to exposures greater than D4 solubility, small sample sizes due to fish mortality (Dow Corning 1992), experimental design issues (Xue et al. 2019, 2020), and dietary D4 studies that could have variable dissolved organic matter in the water to which D4 could adhere. Regardless, there some BCF values appear to be comparable (Fackler et al. 1995).

Given the uncertainties in aquatic biota data collection without co-located water and sediment data from the ECA field study, a BCF based on those data would be uncertain. The use of the BCF (rather than the BAF) is well justified, yet the uncertainty of field data stems from a lack of release data, transfer, and analytical environmental media data. The variability stems from site-specific conditions that can affect body burdens (organic carbon content, pH, temperature, etc.). Without the collection of more data, there are few alternatives other than conducting a more detailed uncertainty analysis that is checked with other models and comparing those results with analytical body burdens.

In addition to the draft charge question 7a Committee comments, it is appropriate to exclude studies where exposure concentrations are greater than D4's water solubility (Dow Corning 1984; Springborn Laboratories 1991b, c). EPA's review of the other BCF studies appropriately identified their limitations. It is important to note that this exclusion of studies conducted above solubility limits relates to BCF determination alone (not toxicity of accumulation studies). The field study within the ECA reports (ERM, 2017) D4 concentrations in wastewater effluents above the EPA selected water solubility of 56 ug/L. So,

there is the potential for D4 to exist in waters above the solubility limit. There are also other field measurements that demonstrate D4 in surface waters at concentrations above the solubility limits, which likely involve microdroplets, surface films, DOC-facilitated dissolution, or sorption to suspended organic carbon (Zhang et al. 2018).

The two field studies cited in Table 3-1 of *Draft Physical Chemistry and Fate Assessment for D4* for estimating BAF for D4 are limited in their applicability. They are both the same species (carp) and analyzed only muscle, not whole fish. EPA correctly noted this is a significant limitation as fish species vary in their percent lipid, size, diet, and metabolism.

In terms of uncertainties, the SACC has concern with the lipid normalization of measured BCFs used to derive a "representative, central-tendency BCF" (US EPA 2025g, 41–42, and Appendix B.2). While it is true that lipid normalization has historically been applied to some chemicals, it is not mechanistically appropriate to assume BCF scales with lipid content for *all* substances, especially those for which there is no evidence that they partition predominantly into the fat tissue rather than other tissues. In the case of D4, Table Appendix B-1 (US EPA 2025g, 76–77) clearly shows no clear correlation between wet-weight BCF and lipid content, indicating lipid is not the primary driver of BCF. Therefore, applying lipid normalization to D4 BCFs is not substantiated by the available evidence and should not be used.

In addition, if EPA intends to apply lipid normalization to D4 BCFs, it is important to ensure that both the lipid content data and the BCF values are derived from the same test population. Currently, the lipid content used to scale two data points from Dow Corning (1992) and Dow Corning (1993) (see Table Appendix B-1) are drawn from studies published in 2007 and 2024. These later studies may not accurately represent the lipid content of the original test populations, which may introduce inconsistency and uncertainty into the normalization process.

The SACC recommends that EPA adopt mechanistic, scenario-based bioaccumulation modeling to derive a representative central-tendency and the UCL_{95} BCF values, rather than pooling literature-reported measured BCFs together and scaling them by lipid content. Instead, measured BCFs should primarily be used to evaluate model performance. In fact, EPA has already demonstrated this approach using the ADME-B model and noted that "the semi-empirical ADME-B BCF of 8,429 L/kg agrees well with the central tendency of the empirical values, of which the arithmetic mean is 8,795 L/kg" (US EPA 2025g, 82). EPA should consider applying a UCL_{95} or higher model-derived value for decision making.

Finally, when using literature-reported measured BCFs to evaluate model performance, the EPA should explicitly weigh data quality. For example, although the *Draft Physical Chemistry and Fate Assessment for D4* clearly acknowledges significant methodological flaws in Xue et al. (2019, 2020) (see Section 3.6.1), those measurements were still included in pooled summaries (see Appendix B.2). The SACC strongly recommends that EPA re-evaluate data quality and exclude or down-weight flawed measurements before using them to support regulatory conclusions.

Specific Comments

The *Draft Physical Chemistry and Fate Assessment for D4* cites three high-quality laboratory studies in which fish (rainbow trout, *Onycorhynchus mykiss*) were fed D4-containing diet and a BMF was calculated

when at steady state (US EPA 2025g, 45). It is not clear why EPA did not include the Woodburn et al. (2013) and Compton (2019) studies in the calculation of the BCF in Table 3-1, similar to the Cantu et al. (2024) study.

Rapid hydrolysis of D4 to DMSD is predicted in an aquatic environment, varying with pH and temperature (US EPA 2025g, 7). This raises the question of potential adverse effects from DMSD, and the uncertainty of potential concentrations of DMSD aquatic environments.

Application of sludge to surface soils and other inputs of of D4 to soil require more attention. Models show that DMSD is produced and also volatilizes under drying conditions, possibly contributing to deposition in streams (Ramanathan et al. 2012). DMSD was found in water in a sequestered system in the International Space Station from cosmetics and other personal hygiene productions (Muirhead and Carter 2018). This example shows release of an active metabolite that could also contribute to DMSD in landfill and wastewater. There is uncertainty due to removal processes in wastewater operations, and few data are available about this metabolite. However, there is evidence from laboratory studies for adverse effects of DMSD on liver, blood cells, and possible neural systems (see Ramanathan et al. 2012; SEHSC 2009; 2007).

Recommendations

- Do not lipid normalize D4 data for BCF calculations unless clear justification can be provided that D4 partitions much more extensively to lipid than to other biological material.
- Consider tabulating modeled biota estimates with available collected data (from Section 3.1 in the *Draft Environmental Exposure Assessment for D4*). Assess the variability in those data and consider the use of other models to estimate bioaccumulation (BCF; as those stated in the comments from Dr. Gobas).
- Provide qualitative statements or indications regarding the general magnitude and direction of how the calculated value is likely to represent reality.

Minor and Editorial Comments

In the *Draft Physical Chemistry and Fate Assessment for D4*, it seems that appended tables B-1 and B-2 (pages 76–77 and 77–78, respectively) are repeated on pages 79–81. Further, they are irrelevant to the content discussed on those pages.

Charge Question 7b.ii

Please comment on the strengths and uncertainties pertaining to EPA's preliminary conclusions surrounding biomagnification metrics

Supporting Evidence for the EPA Preliminary Conclusions

The strengths supporting EPA's conclusions regarding the probability for biomagnification reside in experimental uptake data for fish were used to predict ADME with multicompartment models (e.g., Cantu et al. 2024). These data found that 22 percent was eliminated via feces and not absorbed; 62 percent was biotransformed in gastrointestinal tract; and 16 percent was absorbed (10 percent of this

was biotransformed in the body), leaving a 6 percent bioaccumulation. These data support the lack of biomagnification of D4 from aquatic exposures and are likely relevant for transfer to the terrestrial environment also as often many of these same microflora and digestive enzymes are conserved across species. The field data of D4 body burdens collected from other species are not robust but generally support this conclusion.

In addition, EPA asserts that "While BMF may be estimated from field measurements, controlled laboratory experiments allow the following conditions of an accurate BMF determination to be confirmed: that steady state is reached, that diet is the sole source of exposure to the predator, and that a consistent chemical dose to the predator is maintained." (US EPA 2025g, 44–45).

EPA's preliminary conclusion that D4 does not biomagnify is generally supported by the better-quality evidence. First, the *Draft Physical Chemistry and Fate Assessment for D4* synthesized literature-reported values and showed laboratory dietary BMFs < 1 in all three "high quality" (the term used by the EPA) studies that follow the Organisation for Economic Co-operation and Development Test Guideline 305. Second, the *Draft Physical Chemistry and Fate Assessment for D4* acknowledges that some field TMFs >1 occur but are "relatively close to one" (US EPA 2025g, 46–47). Similarly, the *Draft Environmental Exposure Assessment* finds that "Mean TMF for aquatic biota from seven studies with medium and high data quality was 0.79 (range: 0.31–1.4)" (US EPA 2025c, 17), with only two measurements suggesting TMF>1. More importantly, the *Draft Environmental Exposure Assessment for D4* clearly states that the two TMF>1 measurements are not statistically significant ($p = 0.16$ and $p = 0.23$, respectively) (US EPA 2025c, 17). Therefore, the above lines of evidence indicate no biomagnification.

Potential Issues with EPA's Preliminary Conclusions

EPA heavily relied on laboratory studies and excluded most field studies when determining the aquatic biomagnification metrics (US EPA 2025g, 47). EPA posited that field studies are more uncertain (i.e., less reliable) because of small sample sizes, uncertainties around diet, multiple exposure routes, unknown steady state conditions, and low concentrations (i.e., high percentage on non-detects). However, EPA did not list the uncertainties of laboratory studies, which might include unrealistically high exposures, abnormal diets (e.g., laboratory "fish food") with differing lipid concentrations, non-steady state conditions, small sample sizes (or incorrect replication), nonrepresentative water temperatures, among others. Although EPA states that "… both laboratory- and field-measured bioaccumulation metrics were considered in the overall analysis of the bioaccumulation potential of D4," the lab-derived values were obviously favored (US EPA 2025g, 47).

It is critical to note that field-derived values are more representative of the conditions (temperature, organic carbon, lipid concentrations) that would be encountered in real-world situations. Some studies did describe trophic relationships using $\delta^{45}N$ isotopes (see, for example, Dow Corning 2009). While concentrations in a river or lake may vary over time, this is not likely to occur quickly due to sediment load, so it can be assumed that fish are in a steady state (exposed for approximately 21 days). Laboratory studies can provide insight into processes, contributions of different exposure routes, etc. But if lab-derived values differ significantly from field-derived values, the field-derived values should be given

preference. (EPA eventually did this when assessing risks from fish consumption, defaulting to measured values from the ECA study.)

The Committee appreciates the detailed analysis of statistical significance in the *Draft Environmental Exposure Assessment for D4*; however, some mention of these statistical results should appear in the *Draft Physical Chemistry and Fate Assessment for D4,* as well.

The Committee also noticed and concurred with the public comments submitted by Dr. Frank Gobas. In his comments, he correctly described the uncertainties associated with the less reliable, low-quality data points, e.g., small trophic span, inadequate sample sizes, and incorrect use of lipid normalized BMF_k values, whereby he further argued the importance of selecting only high-quality data for further improvement of the biomagnification assessment. The SACC recommends the EPA adopt these comments.

As captured above, the variation in field collected samples introduces uncertainty in determining biomagnification metrics, with many influencing factors, such as uncertainties related to environmental conditions, bioavailability, source, distance, and concentrations of D4 in aquatic waters, solubility, and transformation products. All are important to assessing the true risk to living organisms. As shown in Table 3-3 and discussed in Section 3.3 of the *Draft Physical Chemistry and Fate Assessment for D4*, the half-life of D4 is also a factor in the environment. Accordingly, data are needed to address potential trophic effects from transformation products and whether these chemicals, in addition to the parent compound D4, exacerbate potential effects from exposure. If the parent compound and the transformed products are considered, then discernable biomagnification may occur.

Further, the strength of laboratory studies is to control variables to the extent possible. As such, it is important to conduct these more controlled studies and then compare them to outcomes from field studies and identify the factors that add uncertainty in the field. Further, modeling and analytics suggested by Dr. Frank Gobal in his public comments (12/2/2025) should be considered by the EPA.

Specific Comments

The discussion of the Biota-Sediment Accumulation Factors (BSAFs) in the *Draft Physical Chemistry and Fate Assessment for D4* is erroneous. EPA states that the BSAF measured by Kent (1994) was not lipid or organic carbon normalized (US EPA 2025g, 44). A BSAF is by definition the ratio of lipid normalized contaminant concentration in tissue divided by the organic carbon normalized contaminant concentration in sediment or soil. The statement cannot be correct. EPA also suggests that BSAFs are above and below the 1.7 threshold (US EPA 2025g, 44). However, the UCL_{90} andUCL_{95} of each BSAF is above the 1.7 threshold, suggesting that D4 bioaccumulation is likely in the environments that were evaluated. Using values below UCL_{90} or UCL_{95} would be inappropriate.

Recommendations

- Tabulate the biomagnification metrics (BCFs, BAFs, BMFs) from all the field studies to see how these data compare to the laboratory data.
- Consider modeling and analytics suggested by Dr. Frank Gobas in his public comments on 12/2/2025.

- Include data that address potential trophic effects from transformation products and whether these chemicals, in addition to the parent compound D4, exacerbate potential effects from exposure. If the parent compound and the transformed products are considered, then discernable biomagnification may occur and should be included in models and assessing risk.

Charge Question 7c

The *Draft Environmental Exposure Assessment for 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 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.

Charge Question 7c.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.

Scientific Rationale

Recent controlled studies evaluating toxicokinetics in fish suggest that a very small proportion of D4 is absorbed via the GI tract in fish (approximately 22 percent is eliminated via feces and not absorbed; 62 percent is biotransformed in the GI tract; and 16 percent is absorbed, 10 percent of which is biotransformed in the body, resulting in 6 percent of D4 oral exposure resulting for bioaccumulation (Cantu et al. 2024) which is supported with data from other studies (e.g., Kim et al. 2025). Trophic transfer should not be discarded simply because the TMF is less than one. EPA should examine the sediment invertebrate data to be sure that the contribution of this food source is, in fact, negligible compared with fish.

Recommendation

The Committee agreed that the EPA should consider exposure of D4 to higher trophic level environmental receptors through bioconcentration of D4 in food items, particularly aquatic organisms; however, biomagnification (i.e., increases of D4 concentration in food items relative to trophic level) is unlikely.

Minority Opinion

The conclusion that D4 is unlikely to bioaccumulate in organisms is supported by the literature as discussed. However, the conclusion that bioaccumulation in higher trophic levels is unlikely is based on a lack of data. Unfortunately, variability associated with field studies also limits the ability to detect potential trophic transfer. These limitations are accompanied by the design concerns and current analyses in the bioaccumulation model, which is for one higher trophic level. Therefore, it is suggested

that EPA consider models containing high trophic level predators, such as scavengers (vultures, racoons, coyotes, etc.). Mink could provide an excellent higher trophic level model but may be only one level removed by consuming exposed fish. In addition, use of more sensitive measures for adverse physiological effects in higher trophic level receptors would indicate potential risk that may not be detected in the current approach.

Charge Question 7c.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.

Scientific Rationale

The Committee generally agreed that there was little scientific support for biomagnification of D4; however, the Committee also agreed that trophic transfer was likely. The Committee generally agreed that the methods and data for estimating dietary exposure for ecological receptors of terrestrial systems are very conservative, which is appropriate for a screening-level assessment. The soil-to-earthworm, short-tailed shrew to the carnivore (bird or mammal) pathway is a standard approach for such assessments. For aquatic-dependent mammals, the pathway of water-to-sediment; chironomids-to-fish-to-American mink is reasonable.

The American mink (*Neogale vision*) was selected as the representative, worse case (exposed) aquatic dependent mammalian species. The mink became the default "aquatic dependent mammal" not only for its fish-, crustacean-, and amphibian-eating habits, but also because it is highly sensitive to reproductive effedts and cancer associated with exposure to polychlorinated biphenyls (PCBs). There are many examples where mink have been used to represent the most sensitive mammal in many Superfund sites containing PCBs, even if they are not the primary contaminant of concern. Toxic sensitivity is not likely the case for D4, but their fish-eating habits and US-wide distribution make them a potential highly exposed species for the screening assessment (as well the availability of life history exposure data from the Wildlife Exposure Factors Handbook). Selection of the shorthead redhorse (*Moxostoma macrolepidotum*) as a representative fish fed upon by mink appears reasonable and is likely a good high-end receptor in regard to sediment exposure. However, the SACC encourages EPA to also consider smaller receptors in the same trophic and foraging guilds with smaller home rages that could have higher exposures (e.g., aquatic insect-arachnids-Carolina Wren).

The methods and data used for estimating dietary exposures for ecologically relevant species are appropriate. Given the interaction of flow and D4 release from industrial or commercial COUs, there will likely be tremendous variability in exposure levels in the field. Accordingly, the emissions to the various areas (land, water, air) will be variable. In addition, the issue raised in charge question 5 highlights the disconnect of D4 concentrations in water versus sediment which would affect dietary exposures.

Estimating dietary exposure based on Equation 5-1 in *Draft Environmental Exposure Assessment for D4* is the standard of practice for wildlife risk assessments. The Exposure Factors in Table 5-1 and Table 5-2 are standard for a screening-level assessment, although the use of juvenile feeding rates for black buffalo

(*Ictiobus niger*) instead of the shorthead redhorse adds uncertainty. Both are in the carp family, and likely have similar feeding habits, but EPA should acknowledge the added uncertainty of this substitution (especially since the lab study utilized juvenile fish).

EPA's assumption of trophic magnification factor of 1 (TMF=1) is acceptable for a screening assessment. Fremlin et al. 2021 showed that this is appropriate for terrestrial systems. The TMF=1 is conservative for the aquatic scenario of sediment to chironomid to fish (Kim et al. 2025 estimate a TMF between 0.1 and 0.3 for D4), but it is acceptable to use it in an initial conservative screening scenario.

EPA concluded that "[t]he overall confidence is robust for biological relevance for the screening-level chronic mammalian assessment using an aquatic-dependent terrestrial species" (US EPA 2025c, 42). This is proceeded by a very important statement that "… the resulting screening-level assessment is protective" (US EPA 2025c, 42). Clearly, conservative assumptions within this analysis are not predictive of wildlife (mammalian) exposure and risk. As long as that distinction remains clear, then EPA can feel confident in concluding that mammalian wildlife is not at risk from exposure to D4.

Although there was general agreement with the conclusions and the methods used, the Committee fundamentally disagreed with the EPA's assertion that somehow only mortality, development, growth are populationally (or ecologically) relevant toxicity endpoints (Draft Risk Evaluation of D4, line 1840, US EPA, 2025h). There are many examples in the literature where regional variation in growth exists to allow a reduced daily food intake to enable reproduction (therefore growth is inhibited) yet no population-level effects occur. This is adaptive and a potential evolutionary mechanism. Certainly, mortality is relevant; however, for many small mammals and birds, lethargy from xenobiotic exposure can be fatal (i.e., adults or offspring become easy prey if lethargic). Moreover, toxicants that influence neurotoxicity or endocrine disruption can affect mate recognition and behavior (including migratory, reproductive, and predator avoidance), territoriality, and have other profound ecological effects.

Additionally, the term "ecologically relevant species" has not been demonstrated. Typically, ecological relevance is defined regarding their relative importance to the community or ecosystem (e.g., keystone species). The use of their exposure templates or life histories are conservative and representative and should be protective of ecologically relevant species in the terrestrial environment given the fate and transport characteristics of D4.

As discussed in the previous charge question 7c.i, the trophic transfer analysis is sound, based on the available literature and current approaches. However, the current models and analyses include one trophic level for estimating transfer. This model ignores higher trophic level organisms and reduces the probability of detecting potential adverse effects on high trophic level organisms, including scavengers. That said, the studies used to assess the potential for trophic transfer are reasonable, with the caveat that Cui et al. 2019 may have overestimated the TMF of 1.4. There is also the question of the findings from experiments using dietary administration of D4 in fish. Finally, transformation products and metabolism of D4 in fish should be considered in any models.

Using the same second-generation inhalation study in rats is appropriate for ecological receptors. However, it is not clear how the toxicity reference value was developed for mammals in the *Draft Risk*

Evaluation for D4 (US EPA 2025h, 89). EPA should use the benchmark dose model to select a BMDL at the 10 percent level and stay away from using the NOAEL or LOAEL if possible. Also, EPA should consider using the second-generation inhalation study (WIL Research 2001) for developing a mammalian inhalation toxicity reference value for burrowing mammals in functionally confined spaces where biosolids are used (e.g., short-tailed shrew, or provide an argument for not doing so.

General Comments

- Please address the lack of concern regarding D4 uptake into plants (vegetables, silage, Fig. 1-4) from biosolid application (Section 3.1.4).
- Additionally, discriminating between environmental exposures and human health hazard appears to be separated and tends to be confusing in Figure 1-2.
- Consider language changes that are more general in support of life history considerations in model selection and refrain from statements regarding ecological relevance and definitive populational relevant endpoints.

Recommendations

- Consider the potential of inhalation exposure via land-application of biosolids as part of the short-tail shrew model. When estimating exposure and risk, refrain from using terms such as "ecologically relevant," which infers ecological function; instead, discuss in terms of exposure (e.g., ecologically representative receptors).
- Address the lack of concern of D4 uptake into plants (vegetables, silage, Fig. 1-4) from biosolid application (Section 3.1.4).
- Consider human exposures from environmental and occupational pathways and labeling ecological hazard to represent environmental exposures to non-human receptors.

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 US 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.

Scientific Rationale

Fish Tissue Concentrations and Use of Modeling versus Field Data

D4 concentrations in fish tissue were modeled by multiplying modeled surface water concentrations by a conservative BCF. This approach likely overestimated tissue residues for several reasons.

First, the laboratory-derived BCF values are based on studies conducted under conditions of low or negligible organic carbon. In natural systems, particulate matter and dissolved organic carbon substantially reduce the bioavailable fraction of D4, leading to lower uptake by aquatic organisms. As a result, application of these BCFs to environmentally realistic waters will tend to overpredict tissue concentrations.

Second, EPA assumed that the BCF remains constant across the full range of water concentrations. For highly hydrophobic chemicals such as D4, this assumption is not well supported. At higher exposure concentrations, effective BCFs may decrease due to sorption, saturation, or other non-linear processes.

A qualitative review of the Effluent Characterization Assessment data indicates that measured organic carbon concentrations in water samples spanned approximately two orders of magnitude, with some of the highest organic carbon values associated with the highest reported D4 concentrations. These conditions would significantly reduce bioavailability and, consequently, tissue uptake. In contrast, some modeled surface water concentrations were based on worst-case assumptions, including 100 percent discharge of waste to surface waters for certain conditions of use and a uniform total organic carbon value across all receiving waters. These assumptions resulted in modeled water concentrations that are higher than would be measured in natural water.

Taken together, the modeled fish tissue concentrations are largely an artifact of multiplying exaggerated water concentrations by an intentionally conservative BCF without accounting for bioavailability. In this context, EPA's decision to default to empirically derived maximum fish tissue concentrations from the ECA for screening purposes is scientifically reasonable.

Variability and Uncertainty in BCFs and Modeled Concentrations

There is substantial variability in reported BCF values for D4 across the literature, likely reflecting its unique fate and transport properties. In addition, some controlled studies rely on radiolabeled compounds, which may not distinguish parent compound from metabolites or transformation products. Modeled concentrations that exceed empirical data by one or more orders of magnitude are often indicative of compounded conservatism rather than realistic exposure scenarios.

Ideally, tissue concentrations would be evaluated alongside co-collected water and sediment samples to enable site-specific bioaccumulation estimates. In the absence of such data, reliance on modeled concentrations with high compounded uncertainty is problematic, and without field data these modeled concentrations would be EPA's best option for evaluating bioaccumulation. Fortunately, EPA required field sampling for D4 in water, sediment, and fish near D4 point sources. Under these circumstances, EPA's decision to rely on empirical upper-bound values rather than modeled outputs is appropriate.

Interpretation of Field Data and Use of Maximum Tissue Concentrations

The general preference for field data over modeled estimates is supported. However, important limitations of the available field data warrant explicit discussion. These include uncertainty regarding the duration of fish residence within wastewater effluent plumes; lack of matched sampling dates for fish, water, and sediment; and the absence of information on fish home ranges relative to plume size and concentration gradients. Fish may have foraged or resided outside the zone of D4 influence, complicating interpretation of tissue concentrations.

Use of the maximum observed fish tissue concentration could be better supported by a quantitative evaluation of uncertainty. For example, calculating the UCL_{95} for the species exhibiting the highest D4 concentration across all sampling locations and comparing that value to the observed maximum would provide insight into whether the maximum plausibly captures the upper tail of exposure. If the maximum substantially exceeds the UCL_{95} (e.g., by an order of magnitude), this would increase confidence that it represents a plausible upper-bound concentration despite spatial and temporal variability.

Information on fish home range, foraging behavior, and habitat use would further support evaluation of whether sampled fish plausibly experienced sustained exposure within the effluent plume.

It is also important to recognize that all grab-sample field measurements represent single points in time and space. Definitive bioaccumulation factors would require controlled or semi-controlled studies with time-integrated determination of D4 concentrations in water and in confined organisms (or those with small and well-defined home ranges), which are generally infeasible for regulatory risk assessments. These limitations reinforce the need for cautious interpretation of both modeled and field-derived values.

Data Quality Considerations for the Maximum Observed Concentration

EPA selected the maximum empirical fish tissue concentration of 14.1 mg/kg as an upper-bound value for screening. This decision is understandable given the large disparity between modeled and measured concentrations. However, the highest value (14.1 mg/kg) is E-flagged as estimated because it exceeds the analytical calibration range and may be biased low due to non-linear detector response at high concentrations (page 17801 of ECA report, volume 2, ERM, 2017). The highest unflagged concentration reported in the same dataset (3.49 mg/kg) is substantially lower (from location DD3; range: 0.123 to 14.1 (E) mg/kg; page 183 of ECA report, volume 1, ERM, 2017).

Nonetheless, additional context supports use of 14.1 mg/kg as a plausible upper bound. The sample was collected near one of a small number of known D4 processing or formulation facilities that discharge treated wastewater directly to surface waters (MPM Silicones, LLC in Friendly, West Virginia). The section of the Ohio River that it discharges into is listed as impaired for bacteria, dioxin, iron, fecal coliform, and PCBs, suggesting elevated and complex environmental stressors. These conditions lend plausibility to the observation of high-end tissue concentrations. On the other hand, EPA states, "… the ECA [data] did not provide any additional information to cross walk these four [monitored] facilities to specific COUs or OESs listed in Table 1-1. The facilities monitored as part of the ECA do not represent all COUs identified in this risk evaluation…" (US EPA 2025d, 53). Notably, monitoring does not seem to adequately represent

media exposed to multiple industrial sources of D4 or other reasonable complex contamination scenarios, limiting their application as representative environmental contamination situations.

Representativeness Versus Plausible Upper-Bound Values

EPA requested input on which fish tissue concentration estimates are most "realistic." The Committee interpreted this to mean representative of the concentrations likely to occur in fish consumed by the populations of interest. Large discrepancies between modeled estimates, ECA monitoring data, and other published monitoring data—spanning multiple orders of magnitude—raise fundamental questions about comparability and representativeness. Notably, the modeled water concentrations of D4 include values which exceed D4's water solubility limit (US EPA 2025d, 53). These modeling results further diminish the credibility of the modeling overall and lend credence to EPA's decision to exclude it for screening purposes.

Regardless, the Committee noted that the ECA data—despite their limitations—may represent the least problematic option for identifying a plausible high-end tissue concentration for screening purposes. However, such a value should not be characterized as "realistic" or "representative" of typical or repeated exposures for the general population or specific subgroups. A plausible upper-bound value is appropriate for an initial screening assessment but should be clearly distinguished from values intended to represent central tendency or frequent exposure.

For assessments intended to characterize representative exposure, use of normative values (e.g., means, medians, or upper confidence bounds around these metrics) is more appropriate. Representativeness infers a characteristic of repetitiveness. Representative values are those that are likely to be found in most of the fish eaten over time, meal after meal. In the general population, the likelihood of buying fish taken from the same waters with the same exposure profile (e.g., same kind and size of fish, same home waters) is extremely unlikely. Therefore, while reliance on high-end values across multiple parameters does not yield a realistic (or representative) exposure scenario and does not compensate for underlying data gaps or uncertainties, the Committee acknowledged its usefulness in screening-level assessments, which is the current state of the D4, due to lack of sufficient release and exposure data for multiple receptors.

Considerations for Tribal Exposure Assessment

The exposure assessment for Tribal populations raises additional concerns regarding relevance and completeness (see US EPA 2025d, 55). EPA's evaluation focused exclusively on fish consumption, despite acknowledging that Tribal communities may experience multiple concurrent exposure pathways. These include consumption of drinking water drawn directly from surface waters, preparation of foods using that water, dermal contact during bathing and swimming, and use of surface waters for cultural, occupational, and ceremonial activities.

The omission of these pathways likely substantially underestimates exposure for Tribal populations, particularly given the potential for repeated and sustained contact with the same contaminated media. Unlike the general population, Tribal diets and water-use practices may involve consistent sourcing from the same environment, increasing the likelihood of chronic exposure. EPA has access to Tribal expertise

and data sources that could inform these pathways and should, at minimum, acknowledge the implications of their exclusion more explicitly.

More broadly, estimating dietary risk for any population based on a single food item is insufficient. It is as if dietary risk for the general population could be divined by considering only fast-food hamburgers. If fish are contaminated, associated water, shellfish, aquatic plants, and terrestrial foods supported by the same environment may also contribute to exposure. As noted in the sections above, benthic organisms may well have higher bioaccumulation than higher trophic level organisms, so shellfish and crustacea would be food types that may contain higher D4 concentrations than fish would contain. Fish consumption is not iconic of all Tribal diets, particularly in the southeast or the arctic, where terrestrial and marine mammals, respectively, feature prominently in Tribal diets. Failure to consider these interconnected pathways limits the realism and completeness of the exposure assessment.

As noted in many previous SACC reviews, calculation of all exposure opportunities with functional aggregate probabilistic models should be done to appreciate the likely risk for the general population or any significant subgroup, especially to a chemical like D4 with the myriads of possible daily exposures.

Recommendations

Modeled D4 Concentrations in Fish

- Refrain from using D4 concentrations fish tissue that are derived from conservative BCFs and unrealistically high surface water concentrations for screening purposes.
- Explicitly acknowledge that modeled concentrations exceeding empirical data by orders of magnitude are artifacts of compounded conservatism.

Use of Empirical Data

- Continue to use ECA fish tissue data to inform screening-level upper-bound exposure estimates, while clearly documenting their limitations.
- Characterize the selected maximum fish tissue concentration as a *plausible high-end screening value*, not as “realistic” or “representative.”

Uncertainty and Statistical Support

- Provide additional quantitative support for use of maximum observed tissue concentrations, such as comparison to species-specific UCL_{95} values.
- Discuss uncertainty related to fish home range, foraging behavior, plume residence time, and the use of grab-sample field data.

Terminology and Risk Communication

- Avoid describing high-end screening values as “realistic” or “representative.”
- Clearly distinguish between values used for conservative screening and those intended to represent typical or repeated exposures.

Representative Exposure Assessment

- For refined or population-representative assessments, use normative tissue concentration metrics (e.g., means, medians, or upper confidence bounds) rather than single maximum values.
- Avoid combining multiple high-end assumptions to estimate exposures intended to represent typical conditions.

Tribal Exposure Assessment

- Expand the Tribal exposure assessment to include relevant additional pathways such as drinking water ingestion, dermal contact, and consumption of other subsistence foods.
- Engage Tribal expertise and existing EPA resources to improve realism, completeness, and transparency of exposure characterization for Tribal populations.
- Acknowledge that estimating dietary risk based on a single food item is insufficient and does not reflect real-world exposure scenarios.
- Identify the need for future assessments to consider aggregate and cumulative exposure pathways, particularly for chemicals such as D4 with multiple daily exposure routes.

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 half-maximal effective concentration (EC_{50}) and the authors did not consider this level of reduction in cell density to be representative of an adverse effect. Therefore, an algae Contaminants of Concern 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.

Scientific Rationale

Aquatic Plants (Algae)

The Committee agreed that the Springborn Laboratories (1990) algal study should not be used to characterize hazard or risk to aquatic plants. While technically well executed, confidence in the environmental relevance of the results is low for several reasons:

- The study relied on a closed system with no headspace, preventing oxygen exchange and creating conditions that do not reflect natural aquatic environments.
- The test substance was maintained at its functional solubility limit, further reducing environmental realism.
- Reduced oxygen availability likely impaired algal growth independently of chemical exposure, making it difficult to attribute observed effects specifically to D4 toxicity.
- Growth rates in the test system were lower than in open-air reference flasks, suggesting that experimental conditions themselves influenced outcomes.
- Based on the fugacity and physicochemical properties of D4, uptake by algae and associated toxicity would be expected to be minimal under environmentally relevant conditions (Fairbrother and Woodburn 2016).

In addition, some fish toxicity studies were conducted under similarly constrained conditions (e.g., reduced headspace and artificially elevated aqueous concentrations). These factors should be clearly acknowledged and discussed in EPA's evaluation of study confidence and relevance.

The Committee noted that reliance on a single algal study provides insufficient information to characterize potential effects of D4 on aquatic plants. Although aquatic plants are ecologically important and more sedentary than fish, the available study does not adequately support risk characterization. Furthermore, reported growth reductions were small and well below levels typically considered indicative of an adverse effect in algal testing (e.g., a 50 percent reduction in growth).

Weight of Evidence and Documentation

Section 3.3 ("Aquatic Plants") of the Technical Support Document lacks a summary table or synthesis of the available body of evidence, unlike other sections of the document. The section begins by identifying a single study as high quality, but it is difficult to determine how this conclusion was reached or whether other available studies were considered. At least one additional vegetation study of medium quality appears to exist.

The Committee recommended clarifying whether only one study was deemed usable, or alternatively, providing a transparent discussion of the full body of evidence and how it informs hazard characterization. Such clarification is particularly important given the potential for overestimation of risk under the experimental conditions used.

Sediment-Dwelling Organisms

The Committee was concerned that risks to sediment organisms may be underestimated due to limitations in the sediment concentration data used in the exposure characterization analysis.

Specifically, measured sediment concentrations exceeded the upper end of the analytical calibration curve by an unknown amount. This limitation compromises data quality and contributes to EPA's conclusion of "slight confidence" in the resulting risk estimates.

Importantly, this uncertainty is directional: it implies a potential underestimation of risk rather than an overestimation. The Committee has previously advised EPA to explicitly state the direction of uncertainty when qualifying confidence in risk conclusions, rather than using equivocal language.

In addition, the Committee noted that reporting hazard quotients only as being greater than 1 does not adequately convey the magnitude of exceedances or the potential severity of risk identified in the aquatic evaluation.

Finally, the Committee requested EPA provide clarification regarding apparent inconsistencies in the reported acute and chronic toxicity thresholds for sediment-dwelling organisms. Acute and Chronic Toxicity thresholds for contaminants of concern to which sediment dwelling organisms are exposed (Tables 4-5 and 4-6 of Enforceable Research Agreement Report by Environmental Resources Management, Inc. (ERM, 2017), seem to be reversed with chronic toxicity occurring at higher concentrations than acute toxicity. An explanation is needed to ensure correct interpretation of these values.

Recommendations

- Do not use the Springborn Laboratories (1990) algal study in the ecological risk assessment.
- Clearly document and justify the basis for excluding this study, including a transparent discussion of its limitations and relevance.
- Improve synthesis and presentation of the body of evidence for aquatic plants, including identification and discussion of all available studies and their influence on hazard characterization.
- Avoid use of the term "conservative" when describing assessments based on potentially unrealistic or worst-case experimental scenarios.
- When describing confidence levels (e.g., "slight confidence"), explicitly state the direction of uncertainty (i.e., whether risk may be underestimated or overestimated).
- Clearly communicate the magnitude of hazard quotient exceedances rather than reporting only whether hazard quotients exceed 1.
- Clarify and explain the relationship between reported acute and chronic toxicity thresholds for sediment-dwelling organisms.

REFERENCES

Andersen ME. (2022). Assessing modes of action, measures of tissue dose and human relevance of rodent toxicity endpoints with octamethylcyclotetrasiloxane (D4). *Toxicology Letters, 357,* 57-72. https://doi.org/10.1016/j.toxlet.2021.12.020

Anderson RA, Millar RP. (2022). The roles of kisspeptin and neurokinin B in GnRH pulse generation in humans, and their potential clinical application. J Neuroendocrinol. 34(5):e13081. Epub 2021 Dec 28. PMID: 34962670. https://doi.org/10.1111/jne.13081

Anthony, T. R, Keil, CB, Simmons, CE,. (2009). Mathematical Models for Estimating Occupational Exposure to Chemicals, 2nd Edition. American Industrial Hygiene Association (AIHA), ISBN #: 978-1-935082-10-1. Edited by Charles B. Keil, Catherine E. Simmons, and T. Renee Anthony. https://stacks.cdc.gov/view/cdc/225248

Biesterbos, JW, Beckmann, G, van Wel, L; Anzion, RB, von Goetz, N, Dudzina, T, Roeleveld, N, Ragas, AM, Russel, FG; Scheepers, PT. (2015). Aggregate dermal exposure to cyclic siloxanes in personal care products: Implications for risk assessment. Environ Int 74: 231-239. http://dx.doi.org/10.1016/j.envint.2014.10.017

Bello, D, Redlich, CA, Stowe, MH, Sparer, J, Woskie, SR, Streicher, RP, Hosgood, HD, Liu, Y. (2008). Skin exposure to aliphatic polyisocyanates in the auto body repair and refinishing industry: II. A quantitative assessment. *Ann Occup Hyg* 52 (2):117–24. https://doi.org/10.1093/annhyg/mem066.

Brown, TN, Armitage, JM, Egeghy, P, Kircanski, I, Arnot, JA. (2016). Dermal permeation data and models for the prioritization and screening-level exposure assessment of organic chemicals. Environ Int 94: 424-435. https://doi.org/10.1016/j.envint.2016.05.025

Brunet CE, Marek, RF, Stanier, CO, Hornbuckle, KC. (2024). "Concentrations of Volatile Methyl Siloxanes in New York City Reflect Emissions from Personal Care and Industrial Use." Environmental Science & Technology 58(20): 8835-8845. https://doi.org/10.1021/acs.est.3c10752

Campbell JL Jr, Andersen ME, Van Landingham C, Gentry R, Jensen E, Domoradzki JY, Clewell HJ 3rd. (2017). Refinement of the oral exposure description in the cyclic siloxane PBPK model for rats and humans: Implications for exposure assessment. Toxicol Lett. 279 Suppl 1:125-135. https://doi.org/10.1016/j.toxlet.2017.04.002. PMID: 28408153

Campbell, J, Andersen, M, Gentry, R, Landingham, CV, Clewell, H. (2023). Incorporation of a recirculating mobile lipid pool description into the cyclic volatile siloxane (cVMS) PBPK model captures terminal clearance of D4 after repeated inhalation exposure in F344 and SD Rats. Toxicol Lett 375: 29-38. http://dx.doi.org/10.1016/j.toxlet.2022.12.014

Cantu MA, Durham JA, McClymont EL, Vogel AH, Gobas FAPC. (2024). Low Dietary Uptake Efficiencies and Biotransformation Prevent Biomagnification of Octamethylcyclotetrasiloxane (D4) and

Decamethylcyclopentasiloxane (D5) in Rainbow Trout. Environmental Science & Technology 58 (23), 10252-10261. http://dx.doi.org/10.1021/acs.est.4c00457

Chang, F., Chen, M, Cheng, S, Shih, T, Mao, I. (2007). Dermal absorption of solvents as a major source of exposure among shipyard spray painters. *JOEM* 49 (4):430–436. *DOI:* 10.1097/JOM.0b013e31803b94ac

Cherrie, JW, Semple, S. (2010). Dermal exposure to metalworking fluids and medium-chain chlorinated paraffin (MCCP). *Ann Occup Hyg* 54 (2):228–35. https://doi.org/10.1093/annhyg/mep081

Christopher, Y., M. Van Tongeren, J. Urbanus, and J. W. Cherrie. (2011). An assessment of dermal exposure to heavy fuel oil (HFO) in occupational settings. *Ann Occup Hyg* 55 (3):319–28. https://doi.org/10.1093/annhyg/mer002

Compton, KL. (2019) Dietary biotransformation and bioaccumulation of cyclic siloxanes in rainbow trout (Oncorhynchus mykiss). (Master's Thesis). Simon Fraser University, Burnaby, British Columbia.

Creta, M., H. Moldovan, K. Poels, S. Voidazan, L. Godderis, R. C. Duca, and J. Vanoirbeek. (2018). Integrated evaluation of solvent exposure in an occupational setting: air, dermal and bio-monitoring. *Toxicol Lett* 298:150–157. https://doi.org/10.1016/j.toxlet.2018.07.049

Cui, S, Fu, Q, An, L, Yu, T, Zhang, F, Gao, S, Liu, D; Jia, H. (2019). Trophic transfer of cyclic methyl siloxanes in the marine food web in the Bohai Sea, China. Ecotoxicology and Environmental Safety, 178, 86,93. https://search.proquest.com/docview/2211945130?accountid=171501

De Vries, TT. (2012). Transferability of aliphatic isocyanates from recently applied paints to the skin of auto body shop workers. *J Occup Environ Hyg* 9 (12):699–711. https://doi.org/10.1080/15459624.2012.728893

Dekant, W, Scialli, AR, Plotzke, K, Klaunig, JE. (2017). Biological relevance of effects following chronic administration of octamethylcyclotetrasiloxane (D4) in Fischer 344 rats. Toxicol Lett.; 279 Suppl 1:42-53. https://doi.org/10.1016/j.toxlet.2017.01.010. Epub 2017 Jan 18. PMID: 28109826.

Delgado, P, Porcel, L. Abril, I, Torres, N, Teran, A, Zugasti, Z. (2004). Potential dermal exposure during the painting process in car body repair shops. *Ann Occup Hyg* 48 (3):229–36. https://doi.org/10.1093/annhyg/meh007

Díaz-González BV, Ramos-Luzardo Á, Henríquez-Hernández LA, Serra-Majem L, Bautista-Castaño I, Acosta-Dacal A, Luzardo OP, Hernández-García E, Cornejo-Torre J, Hernández-Hernández JR, Fernández-Valerón P. (2024). Effect of bariatric surgery in the body burden of persistent and non-persistent pollutants: longitudinal study in a cohort of morbidly obese patients. Front Endocrinol (Lausanne); 22;15:1412261. PMID: 39104810; PMCID: PMC11298429. https://doi.org/10.3389/fendo.2024.1412261.

Domoradzki JY, Sushynski JM, Thackery LM, Springer TA, Ross TL, Woodburn KB, Durham JA, McNett DA. (2017). Metabolism of ^{14}C-octamethylcyclotetrasiloxane ([^{14}C]D4) or ^{14}C-decamethylcyclopentasiloxane ([^{14}C]D5) orally gavaged in rainbow trout (*Oncorhynchus mykiss*). Toxicology Letters 279: 115-124. https://doi.org/10.1016/j.toxlet.2017.03.025

Dow Corning. (1984). Bioconcentration of octamethylcyclotetrasiloxane in fish, with cover letter dated 1761 4/20/94 [TSCA Submission]. (1984-I0030-5721. OTS0558167. 86940001437. 1762 TSCATS/443912). Dow Corning Corp.

Dow Corning. (1992). An 18-day aquatic toxicity test of octamethylcyclotetrasiloxane in rainbow trout 1769 of different size under flow-through saturated conditions (final report) w-attach & letter 042392 1770 [TSCA Submission]. (1992-I0000-37078. 7477. E8385-105. OTS0535642. 86-920000905. 1771 TSCATS/422648). 1772 https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0535642.xhtml 1773

Dow Corning. (1993). A 16-day aquatic toxicity test of octamethylcyclotetrasiloxane in fathead 1774 minnows under flow through conditions at 12 degrees c and with cover letter dated 081693 1775 [TSCA Submission]. (1993-I0000-38306. 7542. OTS0538201. 86-930000377. 1776 TSCATS/424221). HERO ID: 5895957

Dow Corning. (2009). Preliminary assessment of cyclic volatile methylsiloaxane (cVMS) materials in surface sediments, cores, zooplankton, and fish of Lake Opeongo, Ontario, Canada [TSCA Submission]. (HES Study No: 10806-108. 88-100000163. 8EHQ-10-17834A). Centre Europeen 5637 des Silicones (CES).

ECCC (2022).Report of the Board of Review for Decamethylcyclopentasiloxane (Siloxane D5), Environment and Climate Change Canada, Government of Canada. Available at: https://www.canada.ca/en/environment-climate-change/services/canadian-environmental-protection-act-registry/historical/public-consultations/notices-objection/report-board-review-decamethylcyclopentasiloxane-siloxane-d5.html

Eriksson, K, L. Wiklund, L. (2004a). Dermal exposure to monoterpenes during wood work. *J Environ Monit* 6 (6):563–8. https://doi.org/10.1039/B401666C

Eriksson, K., and L. Wiklund. (2004b). Dermal exposure to styrene in the fibreglass reinforced plastics industry. *Ann Occup Hyg* 48 (3):203–8. https://doi.org/10.1093/annhyg/meh012

ERM (2017). D4 Environmental Testing Final Report. Enforceable Consent Agreement (ECA), Environmental Resources Management, Inc., Docket No. EPA-HQ-OPPT-2012-0209, Testing Consent Order for Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2

Fackler, PH, Dionne, E, Hartley, DA, Hamelink, JL. (1995). Bioconcentration by fish of a highly volatile silicone compound in a totally enclosed aquatic exposure system, *Environmental Toxicology and Chemistry*, Volume 14, Issue 10, 1, 1649–1656. https://doi.org/10.1002/etc.5620141004

Fairbrother A, Woodburn KB. (2016). Assessing the Aquatic Risks of the Cyclic Volatile Methyl Siloxane D4. Environ. Sci. Technol. Lett. 10(3):359-363. https://doi.org/10.1021/acs.estlett.6b00341

Fent, KW, Jayaraj, K, Gold, A, Ball, LM, Nylander-French, LA. (2006). Tape-strip sampling for measuring dermal exposure to 1,6-hexamethylene diisocyanate. *Scand J Work Environ Health* 32 (3):225–40. https://doi.org/10.5271/sjweh.1003

Fent, KW, Jayaraj, K, Ball, LM, Nylander-French, LA. (2008). Quantitative monitoring of dermal and inhalation exposure to 1,6-hexamethylene diisocyanate monomer and oligomers. *J Environ Monit* 10 (4):500–7. https://doi.org/10.1039/B715605G

Fent, KW, Trelles Gaines, LG, Thomasen, JM, Flack, SL, Ding, K, Herring, AH, Whittaker, SG, Nylander-French, LA. (2009). Quantification and statistical modeling--part II: dermal concentrations of monomeric and polymeric 1,6-hexamethylene diisocyanate. *Ann Occup Hyg* 53 (7):691–702. https://doi.org/10.1093/annhyg/mep048

Feschuk, A, Kashetsky, N, Chiang, C, Burli, A, Burdick, H, Maibach, H. (2022). Regional variation in percutaneous absorption in in vitro human models: A systematic review. Journal of the American Academy of Dermatology, Volume 87, Issue 3, AB201. https://doi.org/10.1016/j.jaad.2022.06.836

Franzen A, Greene T, Van Landingham C, Gentry R. (2017). Toxicology of octamethylcyclotetrasiloxane (D(4)). Toxicol Lett.; 279 Suppl 1:2-22. https://doi.org/10.1016/j.toxlet.2017.06.007.

Fremlin KM, Elliott JE, Martin PA, Harner T, Saini A, Gobas FAPC. (2021). Fugacity-Based Trophic Magnification Factors Characterize Bioaccumulation of Cyclic Methyl Siloxanes within an Urban Terrestrial Avian Food Web: Importance of Organism Body Temperature and Composition. Environ. Sci. Technol. 2021, 55, 13932−13941. https://doi.org/10.1021/acs.est.1c04269. PMID: 34590828.

Galea, KS, Davis, A, Todd, D, MacCalman, L, McGonagle, C, Cherrie, JW. (2014). Dermal exposure from transfer of lubricants and fuels by consumers. *Journal of Exposure Science and Environmental Epidemiology* 24 (6):665–672. https://doi.org/10.1038/jes.2014.41

Garrod, AN, Martinez, M, Pearson, J, Proud, A, Rimmer, DA. (1999). Exposure to preservatives used in the industrial pre-treatment of timber. *Ann Occup Hyg* 43 (8):543–55. PMID: 10616327

Gijsbers, JH, Tielemans, E, Brouwer, DH, van Hemmen, JJ. (2004). Dermal exposure during filling, loading and brushing with products containing 2-(2-butoxyethoxy)ethanol. *Ann Occup Hyg* 48 (3):219–27. https://doi.org/10.1093/annhyg/meh008

Goede, H, Ploeg, D, Schinkel, J. (2018). *Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek* (TNO) Report: Review of dermal exposure determinants for the dermal Advanced REACH Tool (dART) model.: The Netherlands: Report No. TNO2018 R 10789, March 2018.

Goodman RL, Herbison AE, Lehman MN, Navarro VM. (2022). Neuroendocrine control of gonadotropin-releasing hormone: Pulsatile and surge modes of secretion. J Neuroendocrinol. 2022 May;34(5):e13094. https://doi.org/10.1111/jne.13094. PMID: 35107859; PMCID: PMC9948945.

Guo, WJ, Dai, Y, Chu, XT, Cui, S, Sun, YQ, Li, YF, Jia, HL. (2021). Assessment bioaccumulation factor (BAF) of methyl siloxanes in crucian carp (*Carassius auratus*) around a siloxane production factory. Ecotoxicology and Environmental Safety, 213, 111983. https://doi.org/10.1016/j.ecoenv.2021.111983

Hanssen L, Warner NA, Braathen T, Odland JØ, Lund E, Nieboer E, Sandanger TM. (2013). Plasma concentrations of cyclic volatile methylsiloxanes (cVMS) in pregnant and postmenopausal Norwegian

women and self-reported use of personal care products (PCPs). Environ Int. 51:82-7 https://doi.org/10.1016/j.envint.2012.10.008. PMID: 23201819.

IPCS (2007). Mode of Action Framework. IPCS harmonization project document no. 4. Chemical Safety and Health Unit (CHE). ISBN: 9789241563499. https://www.who.int/publications/i/item/9789241563499

Jandacek, R, Liu, M, Tso, P. (2024). Interactions of Body Weight Loss with Lipophilic Toxin Storage: Commentary, The Journal of Nutrition, Volume 154, Issue 3, 801-803, ISSN 0022-3166. https://doi.org/10.1016/j.tjnut.2024.01.018.

Jia H, Zhang Z, Wang C, Hong, WJ, Sun Y, Li YF. (2015). Trophic transfer of methyl siloxanes in the marine food web from coastal area of Northern China. Environmental Science & Technology. 49(5): 2833-2840. https://doi.org/10.1021/es505445e

Kaj, L, Andersson, J, Cousins, AP, Remberger, M, Brorström-Lundén, E, Cato, I. (2005). Results from 5793 the Swedish National Screening Programme 2004. Subreport 4: Siloxanes. (B1643). Stockholm, 5794 Sweden: IVL Swedish Environmental Research Institute

Kim J, Seston RM, Durham JA, Woodburn KB. (2025). Analysis of temporal trends and accumulation potential of cyclic volatile methyl siloxanes in a temperate freshwater lake ecosystem. Science of the Total Environment 989: 179871. https://doi.org/10.1016/j.scitotenv.2025.179871

Kim J, Xu S, Courtemanche MA. (2025). Modeling of dimethylsilanediol fate and transport in soil. Integr Environ Assess Manag. Sep 1;21(5):1134-1147. https://doi.org/10.1093/inteam/vjaf072. PMID: 40489648.

Krieger, SM, Erskine, TC, Moore, LM. (2021). Octamethylcyclotetrasiloxane (D4): Vapor vs. Aerosol Inhaltinon Study. The Dow Chemical Company, Laboratory Project Study ID: 200014

Lee DH, Porta M, Lind L, Lind PM, Jacobs DR Jr. (2018). Neurotoxic chemicals in adipose tissue: A role in puzzling findings on obesity and dementia. Neurology, 90(4),176-182. PMID: 29358509; PMCID: PMC5798659. **https://doi.org/10.1212/WNL.0000000000004851**

Li, L, Wania, F. (2017). Mechanistic Pharmacokinetic Modeling of the Bioamplification of Persistent Lipophilic Organic Pollutants in Humans during Weight Loss. *Environ. Sci. Technol.* 51, 10, 5563–5571. https://pubs.acs.org/doi/10.1021/acs.est.7b00055

Lindsay, FE, Semple, S, Robertson, A, Cherrie, JW. (2006). Development of a biologically relevant dermal sampler. *Ann Occup Hyg* 50 (1):85–94. https://doi.org/10.1093/annhyg/mei037

Long Y, Jiang M, Gao F, Han M, Gan Q, Zeng F, Zeng S, Hu Y, Dong X, Ye W, Zhu C, Yang H. (2022). The potential risk factors of placenta increta and the role of octamethylcyclotetrasiloxane. Arch Gynecol Obstet. 3:723-734. https://doi.org/10.1007/s00404-021-06335-w. PMID: 34820720.

Marrugo-Padilla A, Atencio-Diaz AB, Barros-Domínguez MF, Guerra-Rivadeneira JD, Hernandez-Cuesta LV, Viloria-Gamez LM. Toxicokinetic Profiles and Potential Endocrine Disruption Effects at the Reproductive

Level Promoted by Siloxanes Used in Consumer Products. J Appl Toxicol. 2024 Jun;45(6):902-915. doi: 10.1002/jat.4706. Epub 2024 Oct 7. PMID: 39375180.

Matsuda F, Ohkura S, Magata F, Munetomo A, Chen J, Sato M, Inoue N, Uenoyama Y, Tsukamura H. (2019). Role of kisspeptin neurons as a GnRH surge generator: Comparative aspects in rodents and non-rodent mammals. J Obstet Gynaecol Res. 45(12):2318-2329. https://doi.org/10.1111/jog.14124. PMID: 31608564.

Matthews JC. (2021). A mechanistic evaluation of the potential for octamethylcyclotetrasiloxane to produce effects via endocrine modes of action. Crit Rev Toxicol. 51(7):571-590. https://doi.org/10.1080/10408444.2021.1994525. PMID: 34877914.

McKim, JM-Jr, Wilga, PC, Breslin, WJ, Plotzke, KP, Gallavan, RH, Meeks, RG. (2001). Potential Estrogenic and Antiestrogenic Activity of the Cyclic Siloxane Octamethylcyclotetrasiloxane (D4) and the Linear Siloxane Hexamethyldisiloxane (HMDS) in Immature Rats Using the Uterotrophic Assay. Toxicological Sciences 63(1), 37-46. https://doi.org/10.1093/toxsci/63.1.37

Meek, ME, Bucher, JR, Cohen, SM, Dellarco, V, Hill, RN, Lehman-McKeeman, LD, Longfellow, DG, Pastoor, T, Seed, J, Patton, DE. (2003). A framework for human relevance analysis of information on carcinogenic modes of action. Crit Rev Toxicol. 33(6):591-653. https://doi.org/10.1080/713608373. PMID: 14727733.

Meeks RG, Jean PA, McNett DA, Plotzke KP. (2022). A 28-day whole-body inhalation study to evaluate octamethylcyclotetrasiloxane (D4) absorption/distribution in two rat strains. Toxicol Lett. 370:53-65.PMID: 36100151. https://doi.org/10.1016/j.toxlet.2022.09.001

Muirhead DI, Carter L. 2018. Dimethylsilanediol (DMSD) source assessment and mitigation on ISS: estimated contributions from personal hygiene products containing volatile methyl siloxanes (VMS). Dean Muirhead, Barrios Technology, Donald Carter, NASA
ICES404: International Space Station ECLS: Systems. 49th International Conference on Environmental Systems, Albuquerque, NM ICES-2018-129. http://hdl.handle.net/2346/74112

NIOSH (2024). National Institute for Occupational Safety and Health About hierarchy of controls. Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/niosh/hierarchy-of-controls/about/index.html [accessed 12/17/25]

OSHA 2023. Identifying Hazard Control Options: The Hierarchy of Controls. Available at: https://www.osha.gov/sites/default/files/Hierarchy_of_Controls_02.01.23_form_508_2.pdf [accessed 12/17/25]

Pauluhn, J. (2021). Inhalation toxicity of cyclic semi-volatile methylsiloxanes: Disentangling the conundrum of phase-specific adaptations from adverse outcomes. Regulatory Toxicology and Pharmacology 122, 104923. https://doi.org/10.1016/j.yrtph.2021.104923

Phanprasit, W., K. Songpek, B. V., and D. Sujirarat. (2019). Inhalation and dermal exposure to toluene among printing workers in a plastic bag factory. *Journal of Health Research* 33 (1):68–79. https://doi.org/10.1108/JHR-06-2018-0031

Plant TM (2012). A comparison of the neuroendocrine mechanisms underlying the initiation of the preovulatory lh surge in the human, old world monkey and rodent. Front. Neuroendocrinol 33, 160-168. https://doi.org/10.1016/j.yfrne.2012.02.002

Plotzke KP, Crofoot SD, Ferdinandi ES, Beattie JG, Reitz RH, Mcnett DA, Meeks RG. (2000a). Disposition of radioactivity in Fischer 344 rats after single and multiple inhalation exposure to[14C]Octamethylcyclotetrasiloxane ([14C]D4). Drug Metabolism and Disposition 28(2), 192-204. Found in references of https://doi.org/10.1177/074823371667006

Plotzke KP, Utell MJ, Looney JR (2000b) Absorption, Distribution and Elimination of 13C-d4 in Humans after Dermal Administration. Report No. 2000-I0000-49147. 2000-09-19. Rochester, NY: University of Rochester Medical Center. Found in references of https://doi.org/10.1177/074823371667006

Pronk, A, Yu, F, Vlaanderen, J, Tielemans, E, Preller, L, Bobeldijk, I, Deddens, JA, Latza, U, Baur, X, Heederik, D. (2006). Dermal, inhalation, and internal exposure to 1,6-HDI and its oligomers in car body repair shop workers and industrial spray painters. *Occup Environ Med* 63(9), 624–31. https://oem.bmj.com/content/63/9/624

Public Law (2016). Frank R. Lautenberg Chemical Safety for the 21st Century Act, An act to modernize the Toxic Substances Control Act, and for other purposes. Public Law 114 – 182, Bill Number: H.R. 2576. https://www.govinfo.gov/app/details/PLAW-114publ182

Quinn AL, Dalu A, Meeker LS, Jean PA, Meeks RG, Crissman JW, Gallavan RH, Plotzke KP. (2007). Effects of octamethylcyclotetrasiloxane (D4) on the luteinizing hormone (LH) surge and levels of various reproductive hormones in female Sprague–Dawley rats. Reproductive Toxicology, 23(4):532-540, ISSN 0890-6238, https://doi.org/10.1016/j.reprotox.2007.02.005

Ramanathan R, James JT, McCoy T. (2012). Acceptable levels for ingestion of dimethylsilanediol in water on the international space station. Aviation, Space, and Environmental Medicine. 83 (6): 598-603. https://doi.org/10.3357/asem.3198.2012. PMID: 22764615

Reddy, MB, Looney, RJ, Utell, MJ, Plotzke, KP, Andersen, ME. (2007). Modeling of human dermal absorption of octamethylcyclotetrasiloxane (D-4) and decamethylcyclopentasiloxane (D-5). Toxicol Sci 99: 422-431. http://dx.doi.org/10.1093/toxsci/kfm174

Roff, MW (1997). Dermal exposure of amateur or non-occupational users to wood-preservative fluids applied by brushing outdoors. *Ann Occup Hyg* 41 (3):297–311. PMID: 9204757

Roff, M., D. A. Bagon, H. Chambers, E. M. Dilworth, and N. Warren. (2004). Dermal exposure to electroplating fluids and metalworking fluids in the UK. *Ann Occup Hyg* 48 (3):209–17. https://doi.org/10.1093/annhyg/meh029

SCCS (2010). Opinion on cyclomethicone octamethylcyclotetrasiloxane (cyclotetrasiloxane, D4) and decamethylcyclopentasiloxane (cyclopentasiloxane, D5), Scientific Committee on Consumer Safety (SCCS/1241/10). https://doi.org/10.2772/24205,

https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_029.pdf

SEHSC (2007). Acute oral toxicity study of dimethylsilanediol (DMSD) in albino rats (up-and-down procedure). Herndon, VA : Silicones Environmental Health and Safety Council (SEHSC), Report No.: WIL-401007.

SEHSC (2009). Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test for dimethylsilanediol in Sprague-Dawley rats via oral gavage. Herndon, VA, Silicones Environmental Health and Safety Council (SEHSC), Report No.: 8EHQ-09-1759. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0604502.xhtml

Semple, S., Graham, M, Cowie, H, Cherrie, J. (2007). The causative factors of dermatitis among workers exposed to metalworking fluids. HSE Research Report RR577. https://www.academia.edu/117065171/The_causative_factors_of_dermatitis_among_workers_exposed_to_metalworking_fluids

Springborn Laboratories. (1990). Octamethylcyclotetrasiloxane - Toxicity to the freshwater green alga, 6064 Selensastrum capricornutum [TSCA Submission]. (90-3-3271. 12023.1288.6103.430. 6065 OTS0557027. 86940000617. TSCATS/442497). Washington, DC: Silicones Health Council. 6066 https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0557027.xhtml

Springborn Laboratories. (1991a). Octamethylcyclotetrasiloxane - the subchronic toxicity to midge 6077 larvae (chironomus tentans) under flow-through conditions [TSCA Submission]. (SLI report 91-6078 3-3698. OTS0557034. 86940000624. TSCATS/442504). Silicones Health Council. 6079 https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0557034.xhtml_6080

Springborn Laboratories. (1991b). (Octamethylcyclotetrasiloxane) – Toxicity test with rainbow trout 6081 (Oncorhynchus mykiss) embryos and larvae [TSCA Submission]. (90-11-3557. 6082 12023.1289.6111.121. OTS0557033. 86940000623. TSCATS/442503). Silicone Health Co. 6083 https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0557033.xhtml_6084

Springborn Laboratories. (1991c). Supplemental study: octamethylcyclotetrasiloxane - the subchronic 6085 toxicity to midge larvae (chironomus tentans) under flow-through conditions (final report) w-6086 cover letter 072691 [TSCA Submission]. (91-7-3813. 12023.1289.6112.128. OTS0531486. 40-6087 9194157. TSCATS/417902). Silicones Health Council. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0531486.xhtml

Tran DN, Park SM, Jung EM, Jeung EB. (2021). Prenatal Octamethylcyclotetrasiloxane Exposure Impaired Proliferation of Neuronal Progenitor, Leading to Motor, Cognition, Social and Behavioral Functions. Int J Mol Sci. 30;22(23):12949. doi: 10.3390/ijms222312949. PMID: 34884750; PMCID: PMC8657511. https://doi.org/10.3390/ijms222312949

Tsukamura H. (2022). Kobayashi Award (2019): The neuroendocrine regulation of the mammalian reproduction. Gen Comp Endocrinol. 315:113755. doi: 10.1016/j.ygcen.2021.113755. Epub 2021 Mar 10. PMID: 33711315. https://doi.org/10.1016/j.ygcen.2021.113755

Urbanus, J., M. Banton, M. Carter, B. Geudens, R. Jones, G. Niemeck, G. Pizzella, R. Tibaldi, and S. Williams. (2014). Dermal exposures associated with service station refuelling activities: preliminary evaluation. CONCAWE report no. 14/14. https://www.concawe.eu/wp-content/uploads/report-no.-14_14.pdf

US EPA (2022). Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities Version 1.0. Office of Chemical Safety and Pollution Prevention. EPA Document # EPA-744-D-22-001. https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0415-0012

US EPA (2024). Draft Considerations and Resources for Assessing Tribal Exposures in TSCA Risk Evaluations. Office of Chemical Safety and Pollution Prevention. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwif98qu04aSAxXJE1kFHdSqKw0QFnoECA0QAQ&url=https%3A%2F%2Fdownloads.regulations.gov%2FEPA-HQ-OPPT-2018-0503-0120%2Fattachment_5.pdf&usg=AOvVaw2TmaPsxAywgQQZBYP0l4j_&opi=89978449

US EPA (2025a). Draft Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for Octamethylcyclotetrasiloxane (D4). Office of Chemical Safety and Pollution Prevention. EPA Document # EPA-HQ-OPPT-2025-1610-0014. https://www.regulations.gov/document/EPA-HQ-OPPT-2025-1610-0014

US EPA (2025b). Draft Consumer and Indoor Dust Exposure Assessment for Octamethylcyclotetrasiloxane (D4). Office of Chemical Safety and Pollution Prevention. EPA Document # EPA-740-D-25-026. https://www.regulations.gov/document/EPA-HQ-OPPT-2025-1610-0019

US EPA (2025c). Draft Environmental Exposure Assessment for Octamethylcyclotetrasiloxane (D4). Office of Chemical Safety and Pollution Prevention. EPA Document # EPA-740-D-25-028. https://www.regulations.gov/document/EPA-HQ-OPPT-2025-1610-0021

US EPA (2025d). Draft Environmental Media and General Population Exposure Assessment for Octamethylcyclotetrasiloxane (D4). Office of Chemical Safety and Pollution Prevention. EPA Document # EPA-740-D-25-027. https://www.regulations.gov/document/EPA-HQ-OPPT-2025-1610-0020

US EPA (2025e). Draft Environmental Release and Occupational Exposure Assessment for Octamethylcyclotetrasiloxane (D4). Office of Chemical Safety and Pollution Prevention. EPA Document # EPA-740-D-25-025. https://www.regulations.gov/document/EPA-HQ-OPPT-2025-1610-0018

US EPA (2025f). Draft Human Health Hazard Assessment for Octamethylcyclotetrasiloxane (D4). Office of Chemical Safety and Pollution Prevention. EPA Document # EPA-740-D-25-030. https://www.regulations.gov/document/EPA-HQ-OPPT-2025-1610-0023

US EPA (2025g). Draft Physical Chemistry and Fate Assessment for Octamethylcyclotetrasiloxane (D4). Office of Chemical Safety and Pollution Prevention. EPA Document # EPA-740-D-25-024. https://www.regulations.gov/document/EPA-HQ-OPPT-2025-1610-0017

US EPA (2025h). Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4). Office of Chemical Safety and Pollution Prevention. EPA Document # EPA-740-D-25-023. https://www.regulations.gov/document/EPA-HQ-OPPT-2025-1610-0005

US EPA (2025i). Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4) Supplemental Information File: Evaluation of Campbell 2023 PBPK Model for Octamethylcyclotetrasiloxane (D4). September. EPA-HQ-OPPT-2025-1610-0031. https://www.regulations.gov/document/EPA-HQ-OPPT-2025-1610-0031

Utell MJ, Gelein R, Yu CP, Kenaga C, Geigel E, Torres A, Chalupa D, Gibb FR, Speers DM, Mast RW, Morrow PE. (1998). Quantitative Exposure of Humans to an Octamethylcyclotetrasiloxane (D4) Vapor. Toxicological Sciences, 44(2):206–213, https://doi.org/10.1093/toxsci/44.2.206

van Wendel de Joode, B., E. P. Bierman, D. H. Brouwer, J. Spithoven, and H. Kromhout. (2005a). An assessment of dermal exposure to semi-synthetic metal working fluids by different methods to group workers for an epidemiological study on dermatitis. *Occup Environ Med* 62 (9):633–41. https://doi.org/10.1136/oem.2004.015396

van Wendel de Joode, B., E. Tielemans, R. Vermeulen, H. Wegh, and H. Kromhout. (2005b). Dermal exposure assessment to benzene and toluene using charcoal cloth pads. *J Expo Anal Environ Epidemiol* 15 (1):47–50. https://doi.org/10.1038/sj.jea.7500349

Vermeulen, R, Lan, Q, Li, G, Rappaport, SM, Kim, S, van Wendel de Joode, B, Shen, M, Bohong, X, Smith, MT, Zhang, L, Yin, S, Rothman, N. (2006). Assessment of dermal exposure to benzene and toluene in shoe manufacturing by activated carbon cloth patches. *J Environ Monit* 8 (11):1143–8. https://doi.org/10.1039/B608076F

Wang, W, Cho, HS, Kim, K, Park, K, Oh, JE. (2021). Tissue-specific distribution and bioaccumulation of cyclic and linear siloxanes in South Korean crucian carp (*carassius carassius*), Environmental Pollution, 288, 17789. https://doi.org/10.1016/j.envpol.2021.117789

WIL Research. (1997a). An inhalation range-finding reproductive toxicity study of octamethylcyclotetrasiloxane (D4) in male rats [TSCA Submission]. (1997-I0000-43725; Study No.: 8462. WIL-51042. OTS0559387. 86-980000049). Dow Corning Corporation. https://hero.epa.gov/reference/7310463/

WIL Research. (1997b). An inhalation range-finding reproductive toxicity study of octamethylcyclotetrasiloxane (D4) in male rats, with cover letter dated 12/3/1997 [TSCA Submission]. (1997-I0000-43726. 8601. WIL-51051. OTS0559399. 86-980000061. TSCATS/445540). Dow Corning Corporation. https://hero.epa.gov/reference/5887603/

WIL Research. (2001). inhalation reproductive toxicity and developmental neurotoxicity study of octamethylcyclotetrasiloxane (D4) in rats, w/cvr ltr dtd 010302 [TSCA Submission]. (2001-I0000-50855. 8713. OTS0574394. 86020000003. TSCATS/454735). Dow Corning Corporation. https://hero.epa.gov/reference/5884077/

Woodburn, K, Drottar, K, Domoradzki, J, Durham, J, McNett, D, Jezowski, R. (2013). Determination of 2279 the dietary biomagnification of octamethylcyclotetrasiloxane and decamethylcyclopentasiloxane 2280 with the rainbow trout (Oncorhynchus mykiss). Chemosphere 93: 779-788. https://doi.org/10.1016/j.chemosphere.2012.10.049

Xu, SH, Chandra, G. (1999). Fate of cyclic methylsiloxanes in soils. 2. Rates of degradation and volatilization. Environ Sci Technol 33: 4034-4039. http://dx.doi.org/10.1021/es990099d

Xue, X; Jia, H; Xue, J. (2019). Bioaccumulation of methyl siloxanes in common carp (cyprinus carpio) 2333 and in an estuarine food web in northeastern China. Arch Environ Contam Toxicol 76: 496-507. 2334 http://dx.doi.org/10.1007/s00244-018-0569-z 2335

Xue, X; Jia, H; Xue, J. (2020). Reply to comment on "Bioaccumulation of methyl siloxanes in common 2336 carp (Cyprinus carpio) and in an estuarine food web in Northeastern China" [Comment]. Arch 2337 Environ Contam Toxicol 78: 174-181. http://dx.doi.org/10.1007/s00244-019-00705-x

Yucuis, R. A., Stanier, C. O., & Hornbuckle, K. C. (2013). Cyclic siloxanes in air, including identification of high levels in Chicago and distinct diurnal variation. *Chemosphere, 92*(8), 905-910. https://doi.org/10.1016/j.chemosphere.2013.02.051

Zhang, Y, Shen, M, Tian, Y, Zeng, G. Cyclic volatile methylsiloxanes in sediment, soil, and surface water from Dongting Lake, China. Journal of Soils and Sediments (2018) 18:2063–2071 https://doi.org/10.1007/s11368-018-1948-9