American Chemistry Council | SEHSC Silicones Environmental, Health, and Safety Center

Via CDX and Electronic Mail

January 28, 2020

Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW (MC-7401M)
Washington, DC 20460

Re: Request for Risk Evaluation under the Toxic Substances Control Act;
Octamethylcyclotetrasiloxane (D4; CASRN: 556-67-2)

Dear Sir or Madam:

Pursuant to § 6(b)(4)(C)(ii) of the Toxic Substances Control Act (TSCA) and 40 C.F.R. § 702.37, *Dow Silicones Corporation, Elkem Silicones USA Corporation,, Evonik Corporation, Momentive Performance Materials, Shin-Etsu Silicones of America, Inc., and Wacker Chemical Corporation*, through the Silicones Environmental, Health and Safety Center (SEHSC), formally request that the U.S. Environmental Protection Agency (EPA or Agency) conduct a risk evaluation of *Octamethylcyclotetrasiloxane (D4; CASRN: 556-67-2)*. The attached document with appendices provides the information required in 40 C.F.R. § 702.37(b) for the submission of a manufacturer request for a risk evaluation. Included with this submission is a draft risk evaluation for D4 that has been prepared in accordance with EPA's *Guidance to Assist Interested Persons in Developing and Submitting Draft Risk Evaluations under the Toxic Substances Control Act, June 2017* for the Agency's consideration as provided for in TSCA § 26(l)(5). This draft risk evaluation addresses the requirements set forth in TSCA § 6(b)(4)(F) and takes into account the scientific standards and weight of the scientific evidence requirements established in TSCA §§ 26(h) and (i).

Should you have any questions or desire further information, please do not hesitate to contact Tracy Guerrero at (202) 249-6196 or tracy_guerrero@americanchemistry.com. We look forward to working with the Agency on this Manufacturer Requested Risk Evaluation.

Sincerely,

Karluss V. Thomas

Karluss Thomas
Sr. Director

Cc: Dow Silicones Corporation
Elkem Silicones USA Corporation
Evonik Corporation
Momentive Performance Materials
Shin-Etsu Silicones of America, Inc.
Wacker Chemical Corporation
Keller and Heckman

Manufacturer Request for Risk Evaluation of Octamethylcyclotetrasiloxane (D4)

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A. Introduction

In 2014, the Silicones Environmental, Health, and Safety Center (SEHSC) entered into the Octamethylcyclotetrasiloxane (D4) (CASRN 556-67-2) Enforceable Consent Agreement (ECA) with the U.S. Environmental Protection Agency (EPA or Agency) to develop environmental exposure data to support a scientifically robust environmental risk assessment for D4. Undertaking such an environmental monitoring program was, to our knowledge, unprecedented under the Toxic Substances and Control Act (TSCA) and an ECA. This agreement was an extension of the silicone industry's voluntary stewardship efforts to support greater scientific understanding of the health and environmental safety of siloxanes used in consumer and industrial applications.

In 2017, the Agency received the Final Report containing the results of the environmental monitoring program conducted pursuant to the ECA. (See docket EPA-HQ-OPPT-2012-0209.) As detailed in the Final Report, the monitoring program resulted in the generation of a robust, valid dataset. Consistent with the design of the program, those data can be used to characterize and understand sources and pathways of the release of D4 to the environment and the resulting environmental exposures to D4.

Following the enactment of the Frank R. Lautenberg Chemical Safety for the 21st Century Act and EPA's issuance of *Procedures for Chemical Risk Evaluations under the Amended Toxic Substances Control Act* (U.S. EPA 2017b), the SEHSC, on behalf of its members, compiled information to support a Manufacturer Request for Risk Evaluation (MRRE) of D4. In addition, a draft risk evaluation for D4 (draft D4 RE) was prepared in accordance with EPA's *Guidance to Assist Interested Persons in Developing and Submitting Draft Risk Evaluations under the Toxic Substances Control Act* (U.S. EPA 2017a) for the Agency's consideration as provided for in TSCA § 26(l)(5). The draft D4 RE, which is included in this document (See **Appendix 2**, the draft D4 RE), addresses the requirements set forth in TSCA § 6(b)(4)(F) and the scientific standards and weight of the scientific evidence requirements established in TSCA §§ 26(h) and (i).

This document with attachments (Submission) provides the information specified in 40 C.F.R. § 702.37(b) for MRREs. The D4 manufacturers making this MRRE (*i.e.*, the Submitting Entities) believe that the contents of this Submission fulfill the requirements for an MRRE of D4 under TSCA and that the Submission is complete and sufficiently robust to enable the Agency to conduct a timely risk evaluation and risk determination on D4.

B. Elements

1. Submitting Entities

Pursuant to 40 C.F.R. § 702.37(b)(1) the following manufacturers of D4, through SEHSC, are formally requesting that the Agency conduct a risk evaluation of D4 for the conditions of use described herein.

- Dow Silicones Corporation
- Elkem Silicones USA Corporation
- Evonik Corporation

- Momentive Performance Materials
- Shin-Etsu Silicones of American, Inc.
- Wacker Chemical Corporation

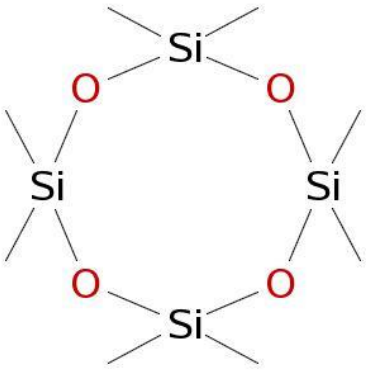
Each of these entities has provided in **Appendix 1** the required Contact Information pursuant to 40 C.F.R. § 702.37(b)(1).

2. Substance Identity

Pursuant to 40 C.F.R. § 702.37(b)(2), the substance that is the subject of this request is D4. D4 is a monoconstituent substance. The following provides the chemical nomenclature and key molecular characteristics to describe D4.

Chemical Name:	Octamethylcyclotetrasiloxane
CAS number:	556-67-2
IUPAC name:	2,2,4,4,6,6,8,8-octamethyl-1,3,5,7,2,4,6,8-tetroxatetrasilocane
Other names:	D4, cyclotetrasiloxane
Molecular formula:	$C_8H_{24}O_4Si_4$
Molecular weight range:	296.61 g/mol

Structural formula:



3. Conditions of Use Requested for Evaluation

Consistent with TSCA § 3(4) and as defined in 40 C.F.R. § 702.33, "conditions of use" means the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of. The conditions of use requested for evaluation in this MRRE are described in Section 4 of the draft D4 RE. In brief, those conditions of use include the

manufacture of D4, processing of D4 as a reactant or by incorporation into a formulation, mixture, or reaction product, and commercial/consumer uses of products that include D4 in their manufacture (*e.g.*, adhesives and sealants, automotive care products, cleaning and furnishing care products, paints and coatings, plastic and rubber products, polishes and sanitation goods, and soaps and detergents) and disposal. Although certain of those uses (*e.g.*, personal care products, food contact materials, and over the counter medication) do not meet TSCA's definition of a "chemical substance," the SEHSC conservatively chose to consider them in the draft D4 RE included with this Submission.

4. Information Relevant to Risk Evaluation

Pursuant to 40 C.F.R. § 702.37(b)(4), an MRRE must include a list of all the existing information that is relevant to whether the chemical substance, under the circumstances identified by the manufacturer(s), presents an unreasonable risk of injury to health or the environment. The list must be accompanied by an explanation as to why such information is adequate to permit EPA to complete a risk evaluation addressing the circumstances identified by the manufacturer(s).

To address this requirement and recognizing that EPA must base its risk evaluations on the "best available science" and the "weight of the scientific evidence" per TSCA §§ 26(h) and (i), a protocol was developed and implemented for the systematic review of information regarding D4. The review, which is based on the Agency's *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA. 2018), focused on information in the following topical areas:

- Physical-chemical properties
- Conditions of Use
- Fate
- Engineering and Exposure
- Human Health Hazard
- Environmental Hazard

A detailed description of the approach and results of the review is provided in the draft D4 RE, Section 2. SEHSC believes that this systematic review process has enabled it to identify sufficient relevant information for the MRRE and to provide a draft risk evaluation for D4 that is consistent with the Agency's goal of "high-quality, fit-for-purpose risk evaluations that rely on the best available science and the weight of the scientific evidence within the context of TSCA." (U.S. EPA 2018).

Physical, Chemical, & Environmental Fate Properties

Relevant information regarding D4 found in the D4 Chemical Safety Report under REACH (CSR), the UK's Environmental Agency's Environmental Risk Assessment D4 (UK EA) and Environment Canada/Health Canada's 2008 Screening Assessment (EC/HC) is presented in the draft D4 RE, Section 3. Physical-chemical properties reported in these sources (physical state, melting/freezing point, boiling point, and density) are considered reliable and were not reviewed further. However, available studies and literature on vapor pressure, water solubility, and partition coefficients were reviewed (see draft D4 RE Appendix B). A summary of the

information on all the above physical-chemical properties is provided in the draft D4 RE, Section 3.

The environmental fate properties of hydrolysis, phototransformation, biodegradation soil sorption and desorption, and bioaccumulation are also reviewed in the draft D4 RE, Section 3.

a. Hazard and Exposure Potential

Information pertaining to any human health hazards of D4 is presented in the draft D4 RE, Section 6.1. This includes a human health hazard assessment that relies on an extensive toxicological database which has been reviewed and assessed in the peer reviewed literature as well as by regulatory authorities. Notably, the hazards identified in the D4 toxicological database occur at high concentrations, which exceed the metabolic capacity of the test systems often leading to secondary nonspecific toxicity. These hazards are therefore conservative endpoints to use in a human health hazard assessment for D4.

Information pertaining to any ecological hazards of D4 is presented in the draft D4 RE, Section 6.2. This includes an ecological hazard assessment that relies on information found in the D4 CSR and the UK's EA. In addition, a literature search was conducted to capture information that has become available subsequent to the publication of these authoritative reviews. Studies and literature that have not been evaluated by one of these authoritative publications were reviewed following the procedure described in the draft D4 RE, Section 6.

Information pertaining to human health exposures to D4 is presented in the draft D4 RE, Section 5.1. This includes a human health exposure assessment that assesses and quantifies the potential exposure of D4 to workers, consumers, and the general population, including those who may be at a greater risk of adverse health effects from exposure. The approach used in the exposure assessment incorporates the requirements set forth in EPA's *Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act* (U.S. EPA 2017b). The exposures are based on conceptual models of D4 worker, consumer, and general population exposure pathways as discussed in the draft D4 RE, Section 4.2.1.

Information pertaining to ecological exposures to D4 is presented in the draft D4 RE, Section 5.2. This includes an ecological exposure assessment that was accomplished using distributions, rather than conservative point estimates, of exposure with measured concentrations of D4 to obtain a realistic view of the probability of harm. This approach is consistent with EPA's stated intent to "strive to utilize probabilistic approaches for exposure assessments used in a risk evaluation" (U.S. EPA 2017b). The approach used in the exposure assessment incorporates the requirements set forth in EPA's *Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act* (U.S. EPA 2017b) moving beyond the standard deterministic hazard quotient technique to incorporate additional advanced methods for characterizing risk. A conceptual model of D4 release and exposure pathways to ecological receptors and key sources of information used for this evaluation are described in the draft D4 RE, Section 4.2.1.

Environmental monitoring data that were collected during a U.S. national monitoring program for D4 under the ECA are utilized in the ecological exposure assessment. The ECA provided

measured concentrations of D4 in the following media: effluent of direct discharge (DD) WWTPs (*i.e.*, those from D4 manufacturer/processor/formulator facilities that have onsite wastewater treatment plants and discharge pursuant to their own permits in lieu of sending effluent to a municipal wastewater treatment facility); influent and effluent of municipal WWTPs; biosolids of municipal WWTPs; and surface water, sediment, and biota (benthic invertebrate and fish species) within the mixing zones of receiving waters.

b. Persistence and Bioaccumulation

Information relevant to the persistence and bioaccumulation of D4 is presented in the draft D4 RE, Sections 3.3.5, 6.2.3, 7.2.6, and 8.2.

P, B and T are considered different but inter-related properties and a conclusion regarding D4 must consider integrating all three properties together and should include all available lines of evidence to determine the real potential for D4 to lead to concerns in the environmental media where it is found. In addition, all papers and reports should be assessed in detail, using pre-defined criteria for quality and relevance to develop scores (on a relative scale) to separate those of greater quality from those of lesser quality and the relevant from the less-relevant results. Inclusion of all the papers and reports should be done to help to reduce selection bias, however a greater weight should be placed on information and data obtained under more relevant environmental conditions.

When using the weight-of-evidence approach as defined by Bridges and Solomon, 2017, and as described above, D4 does not qualify as a persistent, bioaccumulative and toxic (PBT).

Persistence

It is important to understand the overall distribution and fate of D4 in the environment, which is dictated by its unique physico-chemical properties due mainly to the inorganic backbone chain of Si-O-Si units. Since D4 is predominately released to air and will partition readily when released to other compartments to air where it is degraded more rapidly than in other matrices, D4's presence in the environment is much shorter and would be considered easily reversible if sources were to cease. D4 may have a much shorter half-life in air based on actual monitoring data (Xu et al., 2019) and additional work is underway to assess this hypothesis.

D4 is readily degraded by benthic organisms (Selck et al., 2018). As indicated in Selck et al., 2018 "*Persistence is evaluated by measuring the compound's microbial degradation half-lives in water, sediment or soil (in the absence of eukaryotes),* which leads to the conclusion by the authors that *"interactions between microbes and eukaryotes enhance microbial activity, which may further increase microbial degradation, thereby decreasing P below what is measured in standard tests*." Although D4 is persistent in sediment under standardized laboratory testing, this work raises the need for understanding true environmental persistence of D4 under more relevant environmental conditions whereinteractions between microbes and eukaryotes are factored in. In addition although D4 may be present in sediment to some extent but by its nature the sediment does not give an elevated potential for uptake of the strongly-adsorbed D4 into biota. Lastly, benthic organisms are clearly capable of metabolism of D4, and there is no demonstrated toxicity to these organisms so the relevance of meeting a bright line criteria in a standard laboratory test is questioned.

An additional publication also questions the persistence of D4 based on multi-media modelling (Kim et al., 2018). In case of a cessation of emissions, modelling studies generally show a relatively fast initial reduction in concentrations even in sediment, which is caused by the degradation of airborne D4. Monitoring data from a measurement campaign in Lake Storvannet Norway (Krogseth et al., 2014) clearly demonstrated while there were detectable levels of D4 emitted into the lake, lake water concentrations of D4 were below Level of Detection (LOD) and D4 was not detected in surface sediments in the lake. This illustrates that D4 residence time in the water/sediment phase is not long.

Bioaccumulation

The available data with regard to the assessment of the bioaccumulative ("B") criterion for D4 comprise laboratory studies of the bioconcentration factor (BCF) and the biomagnification factor (BMF), laboratory and field studies of the biota-sediment accumulation factor (BSAF), and field studies of the trophic magnification factor (TMF).

Dietary biomagnification is the main route of uptake for bioaccumulation of highly lipophilic substances, as research indicates that at naturally-occurring food/water concentration ratios, uptake of highly lipophilic chemicals (i.e., log KOW >6) from water into biota is low compared to uptake via consumption of contaminated foodstuffs, with the importance of dietary uptake increasing with increasing lipophilicity (Thomann, 1989; Qiao et al., 2000). Uptake via water may be an important exposure route in aquatic ecosystems for lower trophic level species, but uptake from food becomes increasingly more significant as trophic position increases. Other data demonstrates that fish are able to significantly eliminate and metabolize D4 from their tissues (Domoradzki et al., 2015, a, b, c), which supports field studies (Powell et al. 2009, Powell et al. 2010, McGoldrick et al. 2014) and modelling (Kim et al. 2015) demonstrating that food web biomagnification of D4 does not occur. Field studies that demonstrate biomagnification of D4 (Borgå et al. 2012, Borgå et al. 2013, Jia et al. 2015) appear to have been strongly biased by variable exposure of food web organisms that migrate across concentration gradients in the study areas (Kim et al. 2015). Consequently, the weight of evidence of the collective information for D4 indicates that food web biomagnification of D4 does not occur in the environment.

It is difficult to clearly interpret a BCF ratio in the context of understanding biomagnification in the environment of highly lipophilic substances. Because of this, the depuration (elimination) and metabolism rates from laboratory studies (in particular, metabolism interpreted from dietary exposures) can be assessed to better predict the behavior of D4 in the environment. Depuration rates show that elimination of D4 from fish is moderately fast (Huggett, 2015, a, b). Depuration rates from sediment organisms may be faster still (Krueger et al., 2010; Selck, 2014). Indeed, based on the collective reliable depuration rates available for D4, the use of elimination half-life as a metric for the bioaccumulation potential of chemicals, as proposed by Goss et al. (2013), indicates that D4 is not likely to bioaccumulate. There is also clear evidence of metabolism of D4 in aquatic organisms (Domoradzki et al., 2015, a, b, c); with a constant metabolism rate (kM) in mature fish of >0.01 d-1 (equivalent to a half-life of <70 days). Modelling (Kim et al. 2015) demonstrates that trophic dilution of D4 (in contrast to trophic magnification) can only occur if D4 undergoes biotransformation. These findings further support the lack of biomagnification potential in the environment

The interpretation of field TMF data available for D4 is complicated by several confounding factors, such as concentration gradients, sediment-water fugacity ratios (Fsw), organism migration, and the biotransformation rate in the ecosystem studied (Kim et al. 2015). In such complex ecosystems TMF will be biased unless these confounding factors are integrated into the TMF calculations.

Bioaccumulation in the environment is a function of bioconcentration and biomagnification and both processes must be taken into consideration when evaluating D4 as a potential B substance. Based on a review of all the lines of evidence, BCF alone is not a reliable indicator of whether the substance in reality poses a risk to the environment. If all influencing factors are considered in the assessment, there is a clear indication that D4 will not biomagnify, but will biodilute in the environment, and therefore D4 should not be considered a potential B substance.

All lines of evidence and the potential concerns for bioaccumulation have been considered. Concerns are highest for lower trophic level species because direct uptake from water is most significant for organisms at lower trophic levels with bioconcentration (i.e. the BCF) being the most significant process of bioaccumulation. Under field conditions uptake from food becomes increasingly more significant as trophic position increases and dietary uptake (i.e. trophic magnification; TMF) will be the key determinant of concentration and possible toxicity in organisms that occupy higher trophic positions, such as fish. As previously discussed, D4 undergoes trophic dilution in the environment and therefore does not represent a concern to higher trophic level organisms.

- Some compounds possess a high BCF without trophic transfer. Although water is an exposure route for lower trophic level organisms, a concern for bioaccumulation would require presence in water, high persistence in water, low potential for elimination from biota at the lower trophic levels and the potential for toxicity to these organisms. These factors are not evident for D4, because the substance is volatile, poorly soluble, and not highly persistent in the majority of natural waters. Its presence in surface water is low to non-existent (Knoerr, 2014), the rate of elimination from biota is moderately high and there is no demonstrated toxicity in aquatic species.
- The substance is persistent in sediment, but sediment does not give an elevated potential for uptake of the strongly-adsorbed D4 into biota. In addition to this, benthic organisms are capable of metabolism (Selck, 2014), and there is no demonstrated toxicity to these organisms (Woodburn and Powell, 2014).

The overall conclusions on the individual parameters based on the above lines of evidence are:

Persistence

- The overall persistence, balanced across all compartments, for the substance is low.

Bioaccumulation

- The substance does not biomagnify in aquatic food chains.
- The substance does not biomagnify in terrestrial food chains.

The overall conclusion is that D4 should not be considered PBT when taking into account all lines of evidence from the robust data available.

c. Potentially Exposed or Susceptible Subpopulations

The human health risk characterization for D4 included in the draft D4 RE integrates the human health hazard and exposure assessments into quantitative assessments of risk for worker, consumer, and general population exposures including potentially exposed or susceptible subpopulations identified as pregnant or lactating women, infants and children, and subsistence fisherman. See the draft D4 RE, Sections 4 – 8 (*i.e.*, §§ 4.2, 4.3, 5.1, 7.1, and 8.3) for further discussion of potentially exposed or susceptible subpopulations.

d. Storage Near Significant Sources of Drinking Water

Information regarding the potential storage of D4 near significant sources of drinking water as identified by the Submitting Entities is being submitted under separate cover directly to the Agency by those companies due to confidentiality claims.

D4 storage locations near significant sources of drinking water typically have spill prevention control and countermeasure plans in place and/or utilize other containment measures or practices to minimize the potential for any accidental releases involving D4 to impact any nearby waters. As noted in the draft D4 RE, Section 5.1.4.2, the presence of D4 in drinking water is considered unlikely based on the physico-chemical properties of the substance (*e.g.*, low water solubility, high volatility, *etc.*). See the draft D4 RE, Section 3.3 for a further discussion of the environmental fate of D4.

It is also noted that D4 is not regulated under any of the following authorities:

- Safe Drinking Water Act (SDWA) - National Primary Drinking Water Regulations (40 C.F.R. Part 141)
- Clean Water Act (CWA) – List of Toxic Pollutants (40 C.F.R. § 401.15)
- Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) – List of Hazardous Substances (40 C.F.R. § 302.4)
- Emergency Planning and Community Right-to-Know Act (EPCRA) – List of Extremely Hazardous Substances (40 C.F.R. Part 355, Appendices A & B)
- EPCRA – List of Toxic Substances (40 C.F.R. § 372.65)
- Clean Air Act (CAA) – List of Regulated Substances for Accidental Release Prevention (40 C.F.R. § 68.130).

The non-listed/regulated status of D4 under the referenced authorities is consistent with a determination that the substance does not pose health or environmental hazards that would warrant concerns if a release were to occur near a significant source of drinking water.

e. Production Volume

The national aggregate production volume of D4 for the years 2012 – 2015 based on information provided to the Agency by industry for the 2016 Chemical Data Reporting (CDR) rule is shown in the table below. Based on those data, no significant change in overall D4 production volume appears to have occurred in the U.S. during the period from 2013 to 2015. Note – it is anticipated that updated production volume data will be submitted by industry, as appropriate and applicable, for the years 2016 – 2019 during the upcoming 2020 CDR reporting period.

Table 1. Production Volume of D4 per CDR Rule Reporting (2012 – 2015)*

Reporting Year	**2012**	**2013**	**2014**	**2015**
Aggregate Production Volume (pounds)	**500,000,000 – 750,000,000**	**750,000,000 – 1,000,000,000**	**750,000,000 – 1,000,000,000**	**750,000,000 – 1,000,000,000**
*** These publicly available data for the 2016 CDR were obtained using EPA's *ChemView* database https://chemview.epa.gov/chemview# [accessed on Oct. 19, 2019]**				

f. Other Information

i. Draft D4 RE

As noted above, the Submitting Entities are providing a complete, draft risk evaluation for D4 as part of this MRRE (see the draft D4 RE). The risk characterization and risk determination included in the draft D4 RE are summarized in Section C, below.

ii. non-VOC

EPA has excluded D4 from the definition of volatile organic compound (VOC) under the federal Clean Air Act (CAA) for ozone control purposes based on a determination that the chemical has negligible photochemical reactivity. *See* 40 C.F.R. § 51.100(s)(1), 59 Fed. Reg. 50693 (Oct. 5, 1994).

iii. Other D4 Assessments

Information on other international assessments on D4 have been provided under Appendix 3a. This information is provided for completeness.

iv. Global Monitoring Data

Appendix 3b provides information on additional studies that reported D4 concentrations in environmental media including, sediment, surface waters, ambient and indoor air, soil, and biota based on samples collected at locations around the world. These data have been included for completeness, but were not included in the draft D4 RE. During the development of the scope of the D4 ECA, the Agency expressed an interest in generating domestic environmental exposure data to support an assessment of the risks to sediment and aquatic-dwelling organisms in the United States from exposure to D4 from domestic sources of the substance. Consequently, those data were used in the draft D4 RE.

5. Commitment to Provide Information

To fulfill the requirement of 40 C.F.R. § 702.37(b)(5), a signed commitment statement is provided in Appendix 1 for each of the Submitting Entities.

6. Scientific Standards

To meet the TSCA science standards, EPA's Office of Pollution Prevention and Toxics (OPPT) has indicated it intends to apply systematic review principles in the development of risk evaluations (U.S. EPA 2018) and strongly recommends that external parties use systematic review approaches when developing draft risk evaluations (U.S. EPA 2017a). Consistent with this approach and as noted under item B.4 above, a protocol was developed for the systematic review of data and information to be used in the preparation of the request for a MRRE and the draft D4 RE (See the draft D4 RE, Section 2).

The key elements of the systematic review process utilized in the preparation of this MRRE and the draft D4 RE included the following:

- A clearly stated set of objectives (defining the question)
- Developing a protocol that describes the specific criteria and approaches that will be used throughout the process
- Applying the search strategy in a literature search
- Selecting the relevant papers using predefined criteria
- Assessing the quality of the studies using predefined criteria
- Analyzing and synthesizing the data using the predefined methodology
- Interpreting the results and presenting a summary of findings.

Specific reference is made to the TSCA science standards in discussions of the data throughout the draft D4 RE. SEHSC believes that the systematic review process resulted in a "high-quality, fit-for-purpose risk evaluation[s] that relied on the best available science and the weight of the scientific evidence within the context of TSCA."

7. Certification

To fulfill the requirement of 40 C.F.R. § 702.37(b)(7), a signed certification is provided in **Appendix 1** for each of the Submitting Entities.

C. Risk Characterization & Determination

The draft D4 RE provided in Appendix 2, which was prepared in accordance with EPA guidance, includes a risk characterization and risk determination for D4 under the specified conditions of use.

With respect to human health, the risk characterization for D4 integrates the human health hazard and exposure assessments into quantitative assessments of risk for worker, consumer, and general population exposures including potentially exposed or susceptible subpopulations identified as women of childbearing age, infants and children, and subsistence fisherman (See

the draft D4 RE, Section 7). Margins of exposure (MOEs) were determined to be greater than the benchmark MOE of 100 for workers, consumers, and the general population who may be exposed to D4 either in the workplace, through the use of consumer products containing D4, or to D4 released in the environment, indicating no unreasonable risk of injury to human health or the environment. The lowest MOE (15,000; 150-fold higher than the benchmark MOE) was estimated for workers engaged in skin care product formulation. Although such products are not relevant under TSCA, these workers serve as an upper bound surrogate for workers involved in the manufacture, processing, and formulation of applicable D4 products.

With respect to potential ecological concerns, the ecological risk characterization includes multiple lines of evidence (LoEs), including: 1) comparing D4 concentrations measured in environmental media to toxicity thresholds derived from laboratory bioassays with sensitive aquatic receptors (fish, invertebrates and plants); 2) comparing D4 concentrations measured in biota tissue to critical target lipid body burden derived from the target lipid model 3) fugacity-based chemical activity assessment; 4) assessing benthic community metrics; and 5) consideration of bioaccumulation potential (See the draft D4 RE, Section 7).

Using multiple LoEs, the ecological risk characterization demonstrates that there is negligible risk from D4 to organisms based on environmentally realistic exposure concentrations. Notably, the ECA monitoring data allowed a conservative risk evaluation to be conducted as the monitoring study collected samples from within the mixing zones at the discharge sites, which compose only a small area of the receiving water ecosystem, and under low-flow conditions.

A Risk Determination for D4 under the specified conditions of use is provided in t, Section 8.3. The draft D4 RE reflects a weight-of-evidence approach and relies on the best available science. As documented in this thorough assessment prepared in accordance with Agency guidance and the mandates of TSCA, D4 does not present an unreasonable risk of injury to human health or the environment under the conditions of use. Risks to workers, consumers, the general population (including potentially exposed sensitive subpopulations), and the environment from D4 were evaluated and not found to be unreasonable.

Appendix 1

Certification, Commitment, and Contact Information of the Submitting Entities

Re: Certification, Commitment, and Contact Information of the Submitting Entity Request for Risk Evaluation under the Toxic Substances Control Act; *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2*

I certify that to the best of my knowledge and belief:

- Dow Silicones Corporation manufactures *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2*.

- All information provided in the "Request for Risk Evaluation under the Toxic Substances Control Act; *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2" (Request)* is complete and accurate as of the date of the request.

- I have either identified or am submitting all information in my possession, control, and a description of all other data known to or reasonably ascertainable by me as required for this request under this part [40 C.F.R. Part 702]. I am aware it is unlawful to knowingly submit incomplete, false and/or misleading information in this request and there are significant criminal penalties for such unlawful conduct, including the possibility of fine and imprisonment.

Pursuant to 40 C.F.R. § 702.37(b)(5) and subject to any data ownership, contractual, or other legal restrictions, Dow commits to provide to the U.S. Environmental Protection Agency any information in its possession referenced in this Request upon request.

As required by 40 C.F.R. § 702.37(b)(1), I am providing the following information:

Dow Silicones Corporation
2200 W Salzburg Rd., Auburn, MI 48611
Michele.Buckingham@dow.com; 989.636.1243

Sincerely,

Michele Buckingham, Director EHS&S, Consumer Solutions

[Printed Name and Title of Authorized Representative of the Member Company]

January 24, 2020

Date Signed

Re: Certification, Commitment, and Contact Information of the Submitting Entity Request for Risk Evaluation under the Toxic Substances Control Act; *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2*

I certify that to the best of my knowledge and belief:

- Elkem Silicones USA Corp. manufactures *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2.*

- All information provided in the "Request for Risk Evaluation under the Toxic Substances Control Act; *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2" (Request)* is complete and accurate as of the date of the request.

- I have either identified or am submitting all information in my possession, control, and a description of all other data known to or reasonably ascertainable by me as required for this request under this part [40 C.F.R. Part 702]. I am aware it is unlawful to knowingly submit incomplete, false and/or misleading information in this request and there are significant criminal penalties for such unlawful conduct, including the possibility of fine and imprisonment.

Pursuant to 40 C.F.R. § 702.37(b)(5) and subject to any data ownership, contractual, or other legal restrictions, Elkem Silicones USA Corp. commits to provide to the U.S. Environmental Protection Agency any information in its possession referenced in this Request upon request.

As required by 40 C.F.R. § 702.37(b)(1), I am providing the following information:

Elkem Silicones USA Corp.
Two Tower Center Blvd., Suite 1802
East Brunswick, NJ 08816
ATTN: J. Christopher York
(732) 227-2060

Sincerely,

J. Christopher York – President, Americas

January 17, 2020
Date

*Elkem Silicones USA Corp. – **Two Tower Center Blvd., Suite 1802 – East Brunswick, NJ 08816***
Tel : 732-227-2060 – Fax: 732-249-7000
silicones.elkem.com

EVONIK
POWER TO CREATE

January 14, 2020

David DelGuercio
Sr. VP & GM Nutrition & Care, NA
Phone +1 804 727 0622
Fax +1 804 727 0843
Mobile +1 804 814 5221
David.DelGuercio@evonik.com

Re: Certification, Commitment, and Contact Information of the Submitting Entity
Request for Risk Evaluation under the Toxic Substances Control Act;
Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2

I certify that to the best of my knowledge and belief:

- Evonik imports *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2.*

- All information provided in the "Request for Risk Evaluation under the Toxic Substances Control Act; *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2" (Request)* is complete and accurate as of the date of the request.

- I have either identified or am submitting all information in my possession, control, and a description of all other data known to or reasonably ascertainable by me as required for this request under this part [40 C.F.R. Part 702]. I am aware it is unlawful to knowingly submit incomplete, false and/or misleading information in this request and there are significant criminal penalties for such unlawful conduct, including the possibility of fine and imprisonment.

Pursuant to 40 C.F.R. § 702.37(b)(5) and subject to any data ownership, contractual, or other legal restrictions, Evonik commits to provide to the U.S. Environmental Protection Agency any information in its possession referenced in this Request upon request.

As required by 40 C.F.R. § 702.37(b)(1), I am providing the following information:

Evonik Corporation
7801 Whitepine Road
Richmond, VA 23237, USA
Technical Contact: Sneha Atwal (804) 727-0681

Sincerely,

David C. DelGuercio 1/14/20

David DelGuercio, Sr. VP & GM Nutrition & Care, NA

January 14, 2020

Evonik Industries AG
Rellinghauser Straße 1-11
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Germany
Phone +49 201 177-01
Fax +49 201 177-3475
www.evonik.com

MOMENTIVE™

Momentive Performance Materials Inc.
260 Hudson River Road
Waterford, NY 12188
momentive.com

Re: Certification, Commitment, and Contact Information of the Submitting Entity Request for Risk Evaluation under the Toxic Substances Control Act; *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2*

I certify that to the best of my knowledge and belief:

- Momentive Performance Materials USA LLC manufactures *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2.*

- All information provided in the "Request for Risk Evaluation under the Toxic Substances Control Act; *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2" (Request)* is complete and accurate as of the date of the request.

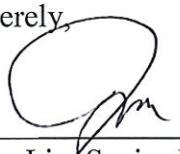
- I have either identified or am submitting all information in my possession, control, and a description of all other data known to or reasonably ascertainable by me as required for this request under this part [40 C.F.R. Part 702]. I am aware it is unlawful to knowingly submit incomplete, false and/or misleading information in this request and there are significant criminal penalties for such unlawful conduct, including the possibility of fine and imprisonment.

Pursuant to 40 C.F.R. § 702.37(b)(5) and subject to any data ownership, contractual, or other legal restrictions, Momentive Performance Materials USA LLC commits to provide to the U.S. Environmental Protection Agency any information in its possession referenced in this Request upon request.

As required by 40 C.F.R. § 702.37(b)(1), I am providing the following information:

Momentive Performance Materials USA LLC
260 Hudson River Road
Waterford, NY 12188
(518) 233-5669

Sincerely,



Jenny Liu, Senior Director, Product Stewardship, Sustainability & Advocacy

1/20/2020

Date Signed

Shin-Etsu Silicones of America, Inc.

1150 Damar Drive
Akron, Ohio 44305
PHONE: (330) 630-9860
FAX: (330) 630-9855

Re: Certification, Commitment, and Contact Information of the Submitting Entity Request for Risk Evaluation under the Toxic Substances Control Act; *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2*

I certify that to the best of my knowledge and belief:

- Shin-Etsu Silicones of America, Inc. manufactures *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2.*

- All information provided in the "Request for Risk Evaluation under the Toxic Substances Control Act; *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2" (Request)* is complete and accurate as of the date of the request.

- I have either identified or am submitting all information in my possession, control, and a description of all other data known to or reasonably ascertainable by me as required for this request under this part [40 C.F.R. Part 702]. I am aware it is unlawful to knowingly submit incomplete, false and/or misleading information in this request and there are significant criminal penalties for such unlawful conduct, including the possibility of fine and imprisonment.

Pursuant to 40 C.F.R. § 702.37(b)(5) and subject to any data ownership, contractual, or other legal restrictions, Shin-Etsu Silicones of America, Inc. commits to provide to the U.S. Environmental Protection Agency any information in its possession referenced in this Request upon request.

As required by 40 C.F.R. § 702.37(b)(1), I am providing the following information:

Shin-Etsu Silicones of America, Inc.
1150 Damar Drive, Akron, OH 44305
Ms. Alexandra Rinehart, Environmental & Regulatory Supervisor

Sincerely,

Kazuhiro Kitani

Kazuhiro Kitani, President and CEO

January 16, 2020

Date Signed

DAVID WILHOIT
PRESIDENT & CEO

Wacker Chemical Corporation
3301 Sutton Road
Adrian, MI 49221, USA
Tel. +1 517 264 8100
David.Wilhoit@wacker.com

January 7, 2020

VIA CDX

Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW (MC-7401M)
Washington, DC 20460

RE: **Certification, Commitment, and Contact Information of the Submitting Entity Request for Risk Evaluation under the Toxic Substances Control Act; *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2***

I certify that to the best of my knowledge and belief:

- Wacker Chemical Corporation (Wacker) manufactures *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2.*

- All information provided in the "Request for Risk Evaluation under the Toxic Substances Control Act; *Octamethylcyclotetrasiloxane (D4) CASRN: 556-67-2" (Request)* is complete and accurate as of the date of the request.

- I have either identified or am submitting all information in my possession, control, and a description of all other data known to or reasonably ascertainable by me as required for this request under this part [40 C.F.R. Part 702]. I am aware it is unlawful to knowingly submit incomplete, false and/or misleading information in this request and there are significant criminal penalties for such unlawful conduct, including the possibility of fine and imprisonment.

Pursuant to 40 C.F.R. § 702.37(b)(5) and subject to any data ownership, contractual, or other legal restrictions, Wacker commits to provide to the U.S. Environmental Protection Agency any information in its possession referenced in this Request upon request.

As required by 40 C.F.R. § 702.37(b)(1), I am providing the following information:

Wacker Chemical Corporation
3301 Sutton Road
Adrian, MI 49221-9397
888-922-5374

Best regards,

David Wilhoit,
President & CEO

Appendix 2

Draft Risk Evaluation for Octamethylcyclotetrasiloxane (draft RE D4)

Exponent

Risk Evaluation for D4 (Octamethylcyclotetrasiloxane)

Exponent

Final

Risk Evaluation for D4 (Octamethylcyclotetrasiloxane)

Prepared for

Allison Starmann, Esq.
American Chemistry Council
700 2nd Street, NE
Washington, DC 20002

Prepared by

Exponent
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Alexandria, VA 22314

December 20, 2019

Exponent, Inc.

Doc. no. 1701939.001 - 3625

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Acronyms and Abbreviations

AA	antacid
ADME	absorption, distribution, metabolism, and excretion
AF	assessment factor
AG	anti-gas
AUC	area under the curve
BAF	bioaccumulation factor
BCF	bioconcentration factor
BCF_k	kinetic bioconcentration factor
BMD	benchmark dose
BMDL	benchmark dose level
BMF	biomagnification factor
BMF_{kL}	ratio of concentration in fish body (lipid-weight) to concentration in feed (lipid-weight)
BMF_k	kinetic adjusted biomagnification factor
BMF_L	lipid adjusted biomagnification factor
BSAF	biota-sediment accumulation factor
bw	body weight
CDF	cumulative distribution function
CDR	Chemical Data Report
CHO	Chinese hamster ovary
ChV	chronic value
Cmax	peak concentration
CPN	chronic progressive nephropathy
CRF	corticotropin releasing factor
CSR	Chemical Safety Report
CTLBB	critical target lipid body burden
CVD	chemical vapor deposition
cVMS	cyclic volatile methyl siloxanes
D4	octamethylcyclotetrasiloxane (CAS RN 556-67-2)
DO	dissolved oxygen
dwt	dry weight
EC50	concentration of test substance causing a specified effect (e.g., inhibition, immobility) in 50% of a group of test organisms
EC/HC	Environment Canada/Health Canada
ECA	Enforceable Consent Agreement
ECHA	European Chemicals Agency
EFH	Exposure Factors Handbook
EPA	U.S. Environmental Protection Agency
EPT	Ephemeroptera Plecoptera Trichoptera
FDA	U.S. Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
GC	gas chromatography

GC/MS	gas chromatography/mass spectroscopy
GLC	gas-liquid chromatograph
GLP	Good Laboratory Practices regulations
GRAS	generally recognized as safe
HBI	Hilsenhoff Biotic Index
HC_5	the hazardous concentration of a test substance to only the most sensitive 5% of species in a species sensitivity distribution
HEC	human equivalent concentration
HED	human equivalent dose
HPA	hypothalamic-pituitary-adrenal
HPLC	high-pressure liquid chromatography
HQ	hazard quotient
HVR	heat-vulcanizing silicone rubber
ISWS	Internal Standard Working Solution
K_{AW}	partition coefficients for air/water
K_M	metabolism rate constant
K_{OA}	octanol-air partition coefficient
K_{OC}	organic carbon/water partition coefficient
K_{OW}	octanol-water partition coefficient
LC50	concentration of a test substance causing 50% lethality in a group of test organisms
LD50	dose of a test substance causing 50% lethality in a group of test organisms
LH	luteinizing hormone
LOAEC	lowest-observed-adverse-effect concentration
LOAEL	lowest-observed-adverse-effect level
LoE	line of evidence
LOEC	lowest-observed-effect concentration
LOI	loss on ignition
LOQ	limit of quantification
LSR	liquid silicone rubber
MATC	maximum acceptable toxicant concentration
MDL	method detection limit
MLP	mixed lipid pool
MOA	mode of action
MOE	margin of exposure
MOS	margin of safety
MPF	manufacturing, processing and formulation
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
MW	molecular weight
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NO_3	nitrate
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration

NPDES	National Pollutant Discharge Elimination System
O_3	ozone
OARS	Occupational Alliance for Risk Science
OC	organic carbon
OECD	Organisation for Economic Co-operation and Development
OH	hydroxyl
OPPT	Office of Pollution Prevention and Toxics
OSHA	Occupational Safety and Health Administration
OT	on-site treatment
OTC	over the counter
PBPK	physiologically based pharmacokinetic
PCB	polychlorinated biphenyl
PDMS	polydimethylsiloxane
PEC	predicted environmental concentration
POD	point of departure
PPE	personal protective equipment
PRA	probabilistic risk assessment
PVA	polyvinyl alcohol
QA	quality assurance
QAPP	quality assurance project plan
QC	quality control
QWoE	quantitative weight of evidence
RCC	Research and Consulting Company Ltd
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RPD	relative percent difference
RTV	room-temperature vulcanized
SCCNFP	Scientific Committee on Cosmetic Products and Non-Food Products
SCCS	Scientific Committee on Consumer Safety
SEHSC	Silicones Environmental, Health and Safety Council
SI	supplemental information
SIM	selective ion monitoring
SOP	standard operating procedure
TC	total carbon
TIC	total inorganic carbon
THF	tetrahydrofuran
TL	trophic level
TLM	target lipid model
TMF	trophic magnification factor
TOC	total organic carbon
TOM	total organic matter
TSCA	Toxic Substances Control Act
TWA	time weighted average
UK EA	UK's Environmental Agency's Environmental Risk Assessment D4 report
VMS	volatile methylsiloxane
V_{sat}	vapor saturation

VOC	volatile organic carbon
WEEL	workplace environmental exposure level
WWTP	wastewater treatment plant

Executive Summary

As provided for by section 26(l) of the Toxic Substances Control Act, as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act (TSCA), this draft risk evaluation for octamethylcyclotetrasiloxane (CAS RN 556-67-2; referred to hereafter as D4) has been prepared to be consistent with the guidance described in the U.S. Environmental Protection Agency's (EPA), *Guidance to Assist Interested Persons in Developing and Submitting Draft Risk Evaluations under the Toxic Substances Control Act* (U.S. EPA 2017a) and to reflect the considerations set forth in EPA's *Procedures for Chemical Substance Risk Evaluations*" (49 C.F.R. Part 702, Subpart B, 82 Fed. Reg. 33726).

To meet the TSCA § 26(h) and (i) science standards, a systematic review process was utilized to develop information for the fate, hazard, and exposure assessments presented in this risk evaluation. Because D4 has been used widely for more than 40 years in a variety of applications, there are abundant high-quality data available on its physical-chemical and environmental fate properties, uses and occurrence, and ecological and human health hazard. D4 has been the subject of authoritative regulatory reviews conducted by Environment Canada/Health Canada (EC/HC 2008) and the United Kingdom Environment Agency (UK EA; Brooke et al. 2009). In addition, D4 has undergone registration through the European Union's REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) program and a Chemical Safety Report (CSR) has been prepared. Additional risk assessments for D4 have been published in the peer reviewed literature (Gentry et al. 2017; Nusz et al. 2018). These prior assessments inform the risk evaluation conducted herein. The systematic review focused on information that has become available subsequent to the identified authoritative reviews. Procedures for searching, evaluating, and integrating the information were developed and are described herein.

The conditions of use of D4, as further described in Section 4.1, include the manufacture of D4, processing of D4 as a reactant or by incorporation into a formulation, mixture, or reaction product, and commercial/consumer uses of products that include D4 in their manufacture (e.g., adhesives and sealants, automotive care products, cleaning and furnishing care products, paints

and coatings, plastic and rubber products, polishes and sanitation goods, soaps and detergents), and disposal and therefore may have D4 as a residual. Risks were evaluated for human health and the environment by comparing measured or predicted exposures to benchmarks or thresholds for hazard. For the assessment of human health, risks to workers, consumers and general populations were evaluated, including potentially exposed or susceptible subpopulations. For the assessment to the environment, risks to aquatic receptors (both pelagic and benthic) were evaluated. Risks to terrestrial ecological receptors are expected to be much lower than those for aquatic receptors, as exposures are lower based on D4 use patterns and environmental fate properties that minimize persistence in the soil or air; therefore, these risks were not evaluated.

For the assessment of human health risks the following routes of exposure were considered: for workers, inhalation and dermal; for consumers, inhalation, dermal, and ingestion; and for the general population, inhalation and ingestion. For workers, the most conservative exposure was inhalation during formulation of skin care products which are not TSCA-relevant (see Section 4.1.4). The exposure assessments for consumers and the general population were also based on non-TSCA relevant exposures to personal care products, cosmetics, over the counter medication, and food contact materials. The results of a two-generation inhalation reproduction study in rats were used (conservatively selecting from among the endpoints) as the basis for the Point of Departure (POD) and physiologically based pharmacokinetic (PBPK) modeling was used to develop internal dose metrics. The POD for all populations (including children), durations, and routes of exposure was 30 mg-hr/L blood/day, based on the area under the curve (AUC) of free D4 in the blood and on the worst-case assumption of continuous exposure. To evaluate human health risks, the POD dose was divided by the exposure dose and compared to the benchmark Margin of Exposure (MOE). The benchmark MOE for this risk evaluation was 100 based on a 10X uncertainty factor for intra-human variability, 1X uncertainty factor for extrapolation from animal-to-human (based on the use of PBPK data), and 10X uncertainty factor for remaining sources of uncertainty related to the database (such as PBPK modeling based on adults not children, and lack of PBPK modeling for pregnant females). All MOEs were well above the benchmark MOE of 100, indicating no unreasonable risk. The highest risk (lowest MOE) was 15,000 for inhalation exposure of male workers in the formulation of skin

care products. This population was used as the sentinel exposure for all worker scenarios. Risks to consumers were an order of magnitude less than for workers, and risks to the general population were another order of magnitude less than those for consumers Aggregate risks for D4 (workers, consumers, and general population combined) were comparable to worker risk alone, further indicating no unreasonable risk.

For the assessment of environmental risk, direct contact and uptake for aquatic receptors through surface water and/or sediment and indirect exposure through the food chain were considered. The exposure assessment was based on the results of a national-scale monitoring program that measured D4 concentrations in relevant environmental matrices downstream from manufacturing, processing and formulation (MPF) facilities with on-site treatment, municipal wastewater treatment plants (WWTPs) receiving industrial discharges (e.g., D4 reasonably expected in the influent), and municipal WWTPs that did not receive industrial discharges. Data from reliable guideline studies and literature were used to establish hazard thresholds. The risk characterization approach used moved beyond a risk quotient method to incorporate multiple lines of evidence (LoEs) and probabilistic assessment of exposure. The LoEs were: 1) comparing D4 concentrations measured in environmental media to toxicity thresholds derived from laboratory toxicity tests; 2) comparing D4 concentrations measured in biota tissue to the critical target lipid body burden (CTLBB) derived from the target lipid model (TLM); 3) fugacity-based chemical activity assessment; and 4) assessing benthic community metrics.; and 5) consideration of bioaccumulation potential. The results of the weight-of-evidence indicated that concentrations of D4 measured in water, sediment, and tissue samples were below applicable thresholds. Benthic community assessment conducted as part of the monitoring program found no evidence of impact in areas receiving D4 in WWTP discharge. Furthermore, the weight of evidence demonstrates that D4 does not bioaccumulate, with data further indicating that it exhibits trophic dilution rather than magnification. Thus, all five LoEs were in agreement, providing strong evidence of no unreasonable environmental risk from D4.

In summary, the database for D4 is robust, containing reliable studies for physical-chemical, environmental fate, human hazard, and ecological hazard endpoints, with no significant data gaps. Exposures were assessed based on a combination of monitoring and modeling.

Conservative approaches (e.g., inclusion of non-TSCA relevant uses in human health risk characterization, field sampling from mixing zones during low flow conditions in environmental risk characterization, etc.) were used throughout. It can be concluded, with a high degree of confidence, that D4 does not present unreasonable risk of injury to human health or the environment (as described under TSCA), including no unreasonable risk to potentially exposed and susceptible populations identified as relevant, under the identified conditions of use.

1 Introduction

As provided for by section 26(l) of the Toxic Substances Control Act, as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act (TSCA), this draft risk evaluation for octamethylcyclotetrasiloxane (CAS RN 556-67-2; referred to hereafter as D4) has been prepared to be consistent with the guidance described in the U.S. Environmental Protection Agency's (EPA) *Guidance to Assist Interested Persons in Developing and Submitting Draft Risk Evaluations under the Toxic Substances Control Act* (U.S. EPA 2017a) and to reflect the considerations set forth in EPA's Final Rule *Procedures for Chemical Substance Risk Evaluations*" (49 C.F.R. Part 702, Subpart B, 82 Fed. Reg. 33726).

1.1 Regulatory Background

Pursuant to Section 6(b)(4) of TSCA, EPA was required to issue a rule that establishes a process for conducting risk evaluations to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation, under the conditions of use. The components to be included in such a risk evaluation have been outlined in 40 CFR 702.41, namely:

- A Scope, including a Conceptual Model and Analysis Plan;
- A Hazard Assessment;
- An Exposure Assessment;
- A Risk Characterization; and
- A Risk Determination.

This draft risk evaluation contains these elements in subsequent sections. Prior to these sections, a discussion is provided on the systematic review process that was used to gather, evaluate and integrate data/information on D4. This is followed by a review of the physical-chemical and environmental fate properties of D4. The section on scope of the evaluation includes a discussion of the conditions of use for which this risk evaluation is applicable (including conditions of use that are excluded) and a presentation of the conceptual models of human and ecological exposure. The sections on hazard assessment, exposure assessment and risk

characterization are divided into human health and ecological components. The draft risk evaluation concludes with a section on risk determination.

The scientific standards for TSCA risk evaluations are to be consistent with the best available science[1] and decisions are to be based on the weight of the scientific evidence.[2] The definitions for these terms, as provided in the Final Rule, are detailed in the footnotes below. These foundational considerations form the basis for this risk evaluation of D4.

To meet the TSCA science standards, EPA's Office of Pollution Prevention and Toxics (OPPT) has indicated it intends to apply systematic review principles in the development of risk evaluations (U.S. EPA 2018) and strongly recommends that external parties use systematic review approaches when developing draft risk evaluations (U.S. EPA 2017a). The systematic review process used for this risk evaluation is discussed in Section 2.

1.2 Previous Evaluations of D4

D4 has been used widely for more than 40 years in a variety of applications and there are abundant data on its properties, occurrence, and hazard. Information on the hazards, exposure, and risks of D4 have been collated and evaluated in recent authoritative regulatory reviews conducted by Environment Canada/Health Canada (EC/HC 2008) and the United Kingdom

---

1 *Best available science* means science that is "reliable and unbiased." Use of best available science "involves the use of supporting studies conducted in accordance with sound and objective science practices, including, when available, peer-reviewed science and supporting studies and data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data). Additionally, EPA will consider as applicable (1) the extent to which the scientific information, technical procedures, measures, methods, protocols, methodologies, or models employed to generate the information are reasonable for and consistent with the intended use of the information; (2) the extent to which the information is relevant for the Administrator's use in making a decision about a chemical substance or mixture; (3) the degree of clarity and completeness with which the data, assumptions, methods, quality assurance, and analyses employed to generate the information are documented; (4) the extent to which the variability and uncertainty in the information, or in the procedures, measures, methods, protocols, methodologies, or models, are evaluated and characterized; and (5) the extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies, or models."

2 *Weight of the scientific evidence* means "a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study, and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance." Components of risk evaluations will be "fit-for-purpose" in that the depth of the analysis will be commensurate with the nature and significance of the decision.

Environment Agency (UK EA) (Brooke et al. 2009). In addition, D4 has undergone registration through the European Union's REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) program and a Chemical Safety Report (CSR) has been prepared. Additional risk assessments for D4 have been published in the peer reviewed literature (Gentry et al. 2017; Nusz et al. 2018; Woodburn et al. 2018; Nusz et al. 2018). Where applicable, this information and these assessments form the basis for the risk evaluation conducted herein.

2 Systematic Review

2.1 Background

EPA has recommended that external parties use systematic review approaches when developing draft risk evaluations (U.S. EPA 2017a). In addition, it is recommended that a protocol describing the process to be followed should be developed during the scoping/problem formulation phase of the risk evaluation to clearly state the procedures that will be used. Planning the systematic review approaches and methods in advance reduces the likelihood of introducing bias into the risk evaluation process. Systematic review has been defined National Academy of Sciences 2017) as "a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. The goal of systematic review methods is to ensure that the review is complete, unbiased, reproducible, and transparent.''

EPA has stated (U.S. EPA 2018) that the systematic review process should generate "high-quality, fit-for-purpose risk evaluations that rely on the best available science and the weight of the scientific evidence within the context of TSCA" and that the key elements of a systematic review include the following:

- A clearly stated set of objectives (defining the question)
- Developing a protocol that describes the specific criteria and approaches that will be used throughout the process
- Applying the search strategy in a literature search
- Selecting the relevant papers using predefined criteria
- Assessing the quality of the studies using predefined criteria
- Analyzing and synthesizing the data using the predefined methodology
- Interpreting the results and presenting a summary of findings.

A protocol was developed for the systematic review of data and information to be used in the preparation of the risk evaluation dossier for D4. This protocol is attached as Appendix A. Key points are discussed below.

2.2 Approach

Because existing data and information for D4 have been collated and evaluated in recent authoritative regulatory reviews by Canada and the United Kingdom (EC/HC 2008; Brooke et al. 2009), the systematic review for D4 built on those results and focused primarily on information that has become available after those regulatory reviews, e.g. since 2008. In particular, the literature search was restricted to information that has become available since 2008. The literature search looked for information in the following topical areas:

- Physical-chemical properties
- Conditions of Use
- Fate
- Engineering and Exposure
- Human Health Hazard
- Environmental Hazard

The search strategy for each topical area is detailed in Appendix A. The search results underwent screening and were included or excluded according to the process described in Appendix A. Data and information from items retained for full text evaluation were extracted into topic-specific templates which facilitated the evaluation of reliability and the data integration processes.

An approach was developed for evaluating the reliability of studies or reports by assigning a score to each information element within that study or report, on a scale of 1 (high quality) to 4 (unacceptable) and then summing the scores for all of the information elements. The range of total possible scores is provided in each template. The lower the total score, the more reliable the information. These scores are useful for comparing data within a particular topic area but not between topic areas, because different templates were developed for different types of studies, depending on the types of information contained. The approach was designed to provide more detail and be more transparent than the widely-used Klimisch scoring system (Klimisch et al. 1997) which relies heavily on compliance with good laboratory practices (GLP) regulations. The templates also align (although they are not exact replicas) with those developed by EPA (U.S. EPA 2018).

Studies that had been previously evaluated by a recognized authoritative source or peer-reviewed publication were not re-evaluated. These sources included the CSR for D4 (CSR 2018), Bridges and Solomon (2016), and Dekant et al. (2017b). Because different sources used different scoring methods, a "scoring translator" was developed to allow a comparison of studies scored using different approaches. Table 2-1 provides a comparison of scoring systems that have been used for D4 information. In the CSR, the Klimisch system was used, where a score of 1 indicates "reliable without restriction", a score of 2 indicates "reliable with restriction", a score of 3 indicates "not reliable" and a score of 4 indicates "not assignable". Information with a Klimisch score of 4 (K4) may provide supporting information although details are lacking. In the Klimisch system, an overall score is given but individual study elements are not scored. Bridges and Solomon (2016) scored individual study elements for quality (reliability) on a scale of 4 to 0, where 4 was the most reliable. The arithmetic mean of the individual scores was computed as an overall score. If major weaknesses were identified in the study (such as lack of measurement of exposures in a toxicity test) the overall mean score was reduced by a multiplier of 0.5, 0.25, etc., depending on the number of major weaknesses. Relevance was scored separately from quality, and different scoring guides (templates) were developed for different types of studies (e.g., persistence, bioaccumulation, toxicity). The focus of the evaluation by Bridges and Solomon (2016) was on the utility of the studies to assess persistence, bioaccumulation and toxicity properties of cyclic volatile methyl siloxanes (cVMSs). Dekant et al. (2017b) also developed a quantitative weight-of-evidence (QWoE) methodology but for the purpose of assessing confidence in postulated mode(s) of action for adverse effects in mammalian toxicity studies. Studies were scored for quality, with individual elements scored on a scale of 4 to 0 (4 being most reliable) and normalized for the number of elements. There were different criteria (templates) for mechanistic studies in intact animals, mechanistic studies in vitro, and genotoxicity studies. Separate scores for relevance and strength of adverse effects, on a scale of 3 to 0, were determined.

EPA's *Guidance for Systematic Review* (U.S. EPA 2018) provides scoring templates for various types of studies and data. Each element (termed "metric") can be scored on a scale of 1 to 4, with 1 representing high reliability and 4 indicating "unacceptable." This approach uses weighting factors for some of the elements. The scores are summed and normalized, resulting in

an overall score on a scale of 1 to 4, with 1 – 1.7 considered high quality, 1.7 – 2.3 considered medium quality, 2.3 – 3 considered low quality, and 4 considered unacceptable.

For this Risk Evaluation dossier, information elements are scored similarly (scale of 1 to 4) and summed. However, the scores are not weighted or normalized. Because there are a different number of information elements in each type of template, the range of possible scores varies depending on the template used.

Table 2-1. Comparison of scoring systems

Scoring System	Overall Values	Individual Element Scoring	Reliability Meaning
Klimisch (used in CSR)	1 – 4	No	1 is considered high; 3 is low; 4 is not assignable but may be supporting
Bridges and Solomon (2016)	4 – 0	Yes, averaged, multiplier applied for major weaknesses. Separate score for relevance	4 is considered high, 0 is low
Dekant et al. (2017b)	4 – 0	Yes, normalized. Separate score for relevance	4 is considered high, 0 is low
EPA (Systematic Review Guidance)	1 – 4	Yes, summed and weighted / normalized	1 is considered high, 4 unacceptable
D4 Risk Evaluation	Range of values differs by template	Yes, summed, but not weighted / normalized	The lower the score, the better the rating

Table 2-2 presents the range of potential scores for each of the templates prepared for use in the D4 Risk Evaluation, as shown in Appendix A. It also shows how these evaluations can be compared to D4 evaluations completed in other reviews. This provides a means for "translation" of the scoring among the different approaches. In the data integration step, as information was aggregated, the scores from different sources were used to assign reliability categories of high, medium and low. It should be mentioned that due to the abundance of information on D4, there was no need to even consider any studies that would be classified as "not assignable" (Klimisch score 4). It should also be noted that, in addition to the scoring, the reviewer may exercise professional judgment in consideration of why the study may or may not be considered reliable. Finally, in some instances, a particular element in a template was not applicable for the study. Rather than assigning the element a score indicating poor reliability, which would unfairly bias

the study, the element was left unscored and the total possible score adjusted. Only those templates relevant to the information being evaluated were actually used. Completed templates are found in Appendices B (Reviews of Studies on Physical-Chemical and Environmental Fate Properties), C (Reviews of Studies on Mammalian Toxicology and Human Health Exposure), and D (Reviews of Studies on Ecological Hazards). The scores from different sources were considered together to arrive at a conclusion of "high" (color-coded blue), "medium" (color-coded yellow) or "low" (color-coded pink) for the utility of the results. If scoring was not appropriate (such as for a review article), no color was added.

Table 2-2. Scoring system translation

Scoring Range in D4 Risk Evaluation	Template Type	Assignment of score to reliability category	Score used by Bridges and Solomon (2016) or Dekant et al. (2017b)	Klimisch score (used in CSR for D4)	Assigned Reliability Category for D4 Risk Evaluation
7 – 28	Occupational exposure	7 – 13 14 – 21 22 – 28	N/A	1 2 3/4	High Medium Low
7 – 28	Environmental release	7 – 13 14 – 21 22 – 28	N/A	1 2 3/4	High Medium Low
4 – 16	Exposure assessments and risk characterizations/PBPK Modeling	4 – 7 8 – 12 13 – 16	N/A	1 2 3/4	High Medium Low
7 – 28	Life cycle and facility data	7 – 13 14 – 21 22 – 28	N/A	1 2 3/4	High Medium Low
26 – 104	Ecotoxicology	26 – 52 53 – 78 79 – 104	≥3.0 2.0 - 2.9 <1.9	1 2 3/4	High Medium Low

Scoring Range in D4 Risk Evaluation	Template Type	Assignment of score to reliability category	Score used by Bridges and Solomon (2016) or Dekant et al. (2017b)	Klimisch score (used in CSR for D4)	Assigned Reliability Category for D4 Risk Evaluation
18 – 72	Environmental fate: Bioaccumulation, laboratory studies, field studies	18 – 36	≥3.0	1	High
		37 – 54	2.0-2.9	2	Medium
		55 – 72	≤1.9	3/4	Low
21 – 84	Human Health: Animal toxicity	21 – 42	≥3.0	1	High
		43 – 64	2.0 – 2.9	2	Medium
		65 – 84	≤1.9	3/4	Low
23 – 92	Human Health: *In vitro*	23 – 45	≥3.0	1	High
		46 – 67	2.0 – 2.9	2	Medium
		68 – 92	≤1.9	3/4	Low
10 – 40	Monitoring/Bio-monitoring	10 – 20	≥3.0	1	High
		21 – 30	2.0 – 2.9	2	Medium
		31 – 40	≤1.9	3/4	Low
6 – 24[1]	Physical/chemical	6 – 12	≥3.0	1	High
		13 – 19	2.0 – 2.9	2	Medium
		20 – 24	≤1.9	3/4	Low
15 - 60	Physical/chemical: Phototransformation	15 – 29		1	High
		30 – 44	N/A	2	Medium
		45 – 60		3/4	Low
14 - 56	Physical/chemical: Hydrolysis	14 – 27		1	High
		28 – 41	N/A	2	Medium
		42 – 56		3/4	Low
18 - 72	Physical/chemical: Biodegradation	18 – 36		1	High
		37 – 54	N/A	2	Medium
		55 – 72		3/4	Low

[1] Applicable to physical/chemical categories such as sorption/desorption, with the exception of phototransformation, hydrolysis, and biodegradation.

In the data integration stage, reliability, relevance, consistency, coherence, and biological plausibility were considered, as appropriate, to develop a weight-of-evidence argument synthesizing multiple evidence streams. A written summary of the information, identifying key studies, was prepared for each major topical area. Information was also presented at a summary level in tabular format. The actual study evaluations appear in Appendices B, C and D. Each source of information was assigned an ID reference to facilitate tracking.

3 Physical, Chemical, and Environmental Fate Properties

3.1 Overview

Relevant information regarding D4 found in the D4 CSR (2018) under REACH, the UK EA's Environmental Risk Assessment D4 report (Brooke et al. 2009), and EC/HC's 2008 Screening Assessment is presented in Table 3-1 through Table 3-10. Original reports relied upon in the CSR, UK EA, and EC/HC assessment were reviewed when necessary (for example, to resolve any inconsistencies). In addition, studies and literature that are too new to have been included in the three assessments were evaluated and added to the tables. Except for endpoints with consistent and reliable data (as identified below), or those that have been evaluated by another authoritative publication, studies appearing in Table 3-1 through Table 3-10 were reviewed following the procedure described in Section 2 (Systematic Review) and the reviews are attached as Appendix B. Some studies were evaluated by Bridges and Solomon (2016) and these scores are also included.

3.2 Physical-chemical Properties

A number of physical-chemical properties have been previously reported from a collection of sources that are in agreement and are considered reliable data. These properties include physical state, melting/freezing point, boiling point, and density. These properties are summarized in the CSR, UK EA, and EC/HC assessment reports, and in Table 3-1 the original references are listed. These properties were not reviewed further. However, available studies and literature on vapor pressure, water solubility, and partition coefficients were reviewed (Appendix B). A summary of the information on all the above physical-chemical properties is provided in Table 3-1. Other physical-chemical properties are considered inapplicable or irrelevant to D4 and its risk evaluation; therefore, they are not included in Table 3-1 and no additional information was reviewed. These excluded properties are flash point, flammability, explosive properties, self-ignition temperature, oxidizing properties, granulometry, dissociation constant, viscosity, surface tension, stability in organic solvents, and identity of relevant degradation products.

The collection of sources reviewed was used to arrive at the preferred values for the following properties: 1) a melting point of 17.7°C, 2) a boiling point of 175°C at 101 kPa, and 3) a density of 0.95 g/cm^3 at 25°C. Melting point values of 17.7 and 17.5°C are found in collections of data considered reliable. Boiling point data were reviewed by Chandra (1997). Chandra (1997) is part of the collection of reliable information relied upon by the UK EA report, and was not reviewed further. Chandra (1997) reviews the available measured data for numerous physical chemical properties and determines the preferred and most reliable value for each physical chemical property. Per Chandra (1997), the preferred value for boiling point is 175°C. The preferred value for density is 0.953 g/cm^3 at 20°C.

Based on consideration of additional sources, the vapor pressure for D4 ranges from 0.125 to 68 kPa. Chandra (1997) reviewed the available measured data and reported a vapor pressure at 25°C of 0.132 kPa (reported as 0.99 mmHg; ~132 Pa); this value is an interpolated value derived from a temperature–vapor pressure correlation (the AIChE DIPPR method) using data obtained over the temperature range from 17.6 to 313°C (IUCLID 2005) as reported in Brooke et al. (2009) as part of the reliable collection of information on D4. Flaningam (1986) reported a measured vapor pressure for D4 of between 3.36 and 68 kPa over a temperature range of 473–578 K. A more recent study by Lei et al. (2010) using a gas chromatographic retention time technique provides a value of 0.125 kPa (reported as 124.5 Pa at 308–368 K). The preferred value, based on the review by Chandra (1997) as cited in Brooke et al. (2009), is 0.132 kPa at 25ºC.

For water solubility, the identified values range from 0.033 to 0.074 mg/L. GLP studies conducted using a generator column method following TSCA Test Standard 796.1860 provided values of 0.074 mg/L at 24°C in freshwater (Springborn Laboratories, Inc. 1989a; referred to as Springborn subsequently[3]) and 0.033 mg/L at 25°C in seawater (Springborn 1989b). A value of 0.056 mg/L at 23°C was determined by Varaprath et al. (1996) using a non-turbulent slow-stirring method. These studies are all considered reliable; the value from the most recent study (0.074 mg/L for freshwater) was selected as the preferred value.

[3] Springborn refers to both Springborn Laboratories, Inc., and Springborn Smithers Laboratories.

The log of the octanol-water partition coefficient (K_{OW}) has been determined as 6.49 using a slow stirring method (Organisation for Economic Co-operation and Development (OECD) 123; Dow Corning Corporation 2007c) and 6.98 using a syringe method (Dow Corning Corporation 2007d). The log of the measured octanol-air partition coefficient (K_{OA}) is reported as 4.22 (Dow Corning Corporation 2006a). Using a novel 3-phase equilibrium method, Xu and Kropscott (2012) simultaneously determined the partition coefficients for air/water (K_{AW}) as well as K_{OA} and K_{OW}. At an average temperature of 21.7ºC, the results were: log: K_{AW} = 2.69, log K_{OA} = 4.29, and log K_{OW} = 6.98. Xu et al. (2014) discussed the advantages of this method in comparison to the separate determination of partition coefficients and the distribution of cVMSs as predicted by these coefficients: tendency to partition to the air compartment from water and moist soils, and from water to organic carbon. Thus, the Xu and Kropscott (2012) partition coefficients are the preferred values.

Table 3-1. Physical-chemical properties

Method	Property	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from ECHA dossier)	Reference	Reference ID
	Physical state at normal temperature and pressure	Liquid	Liquid at normal temperature and pressure	N/A	N/A	Reliable collection of data includes: IUCLID 2000	EA09A; CSR18A
	Melting / freezing point	Melting point: 17.7°C	Melting point values of 17.7 and 17.5°C are quoted in collections of data which have been subject to peer-review and in which the original data sources are traceable. The results are considered reliable.	N/A	2	Reliable collection of data includes: IUCLID 2005	EA09A; CSR18A
	Boiling point	Boiling point: 175°C	A boiling point of 175°C at 101.3 kPa is reported in two collections of reliable data. Boiling points of 175.5 and 175.6°C are reported in secondary sources to which reliability could not be assigned.	N/A	2	Reliable collection of data includes: Chandra 1997; IUCLID 2000, 2005; Merck 1996; OECD 1995	EA09A; CSR18A
	Relative density	Density: 0.95 g/cm^3 at 25°C	A density value of 0.95 g/cm³ at 25°C is reported in a handbook or collection of reliable data which has been subject to peer-review and in which the original data sources are traceable. The result is considered reliable. Other sources give density values in the range 0.95 to 0.96 g/cm³.	N/A	2	Reliable collection of data includes: IUCLID 2005; Merck 1996	EA09A; CSR18A
Value is derived from a temperature–vapor pressure correlation using critically evaluated data	Vapor pressure	Vapor pressure: 132 Pa at 25°C	A vapor pressure value of 132 Pa at 25°C is reported in a collection of reliable data which has been subject to peer-review and in which the original data sources are traceable. A number of sources to which reliability could not be assigned gave vapor pressure values in the range of 82–96 Pa at 20°C or 132–139 Pa at 25°C.	N/A	2	Reliable collection of data includes: Chandra 1997; IUCLID 2005	EA09A; CSR18A;
Gas chromatographic retention time	Vapor pressure	Vapor pressure of 124.5 ± 6.2 Pa at 308–368K; equivalent to 0.125 kPa.	Publication describing derivation of vapor pressures of cyclic and linear polydimethylsiloxane oligomers.	9	2	Lei et al. 2010	LEI10A
Ebulliometer	Vapor pressure	Vapor pressure ranged between 3.36 and 68 kPa when testing in a range of temperatures from 473 to 578 K	Measured over pressure range of 7–133 kPa and then fitted to Antoine equation. Extrapolations made based on literature and estimated critical constants, Halm-Stiel extension, of Pifzer's vapor equation. Extrapolated data was found to also fit the AIChE DIPPR vapor pressure equation.	6	N/A	Flaningam 1986	FLANI86A

Method	Property	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from ECHA dossier)	Reference	Reference ID
Non-turbulent test: slow-stirring method at 23 °C	Water solubility	Water solubility: 0.056 mg/L at 23°C (GC-MS method); 0.053 mg/L (GLC method)	Two analysis methods were used: a purge and trap method connected to a gas-liquid chromatograph column (GLC) and analyzed by GC-MS and extraction with GLC analysis. The average concentration (by extraction and GLC analysis) was 53.1 ± 6.6 ppb and by purge and trap GC-MS 56.2 ± 2.5 ppb.	6	2	Varaprath et al. 1996	VARAP96A
Generator column method (TSCA Test Standard 796.1860)	Water solubility	Water solubility: 0.074 mg/L at 24°C in freshwater	Guideline study conducted under GLP with well-documented findings.	6	1	Springborn Laboratories, Inc. 1989a (Study Director: Smith)	SPRIN89A
Generator column method (TSCA Test Standard 796.1860)	Water solubility	Water solubility: 0.033 mg/L at 25°C in seawater	Guideline study conducted under GLP with well-documented findings.	6	2	Springborn Laboratories, Inc. 1989b (Study Director: Smith)	SPRIN89B
Slow-stirring Method (OECD 123)	n-Octanol-water partition coefficient (log value)	n-Octanol-water partition coefficient: log *K*ow value of 6.49 at 25°C	Value obtained using a slow-stirring method (draft OECD Guideline) designed to avoid problems associated with hydrolysis of D4. Conducted under GLP.	6	1	Dow Corning Corporation 2007c (Study Director: Kozerski)	DOWCO07E
Two different extraction methods: HPLC with a radiometric detector, and liquid scintillation counting analysis for radioactivity quantification	Partition coefficient n-octanol/water (log value)	*n*-octanol-water partition coefficient: log Kow value of 6.98; log K_{AW} for D4 is 2.69; log K_{OA} for D4 is 4.29 at 21.7°C	A syringe method developed in this work gave a log Kow of 6.98 at 21.7 °C.	7	2	Dow Corning Corporation 2007d (Study Directors: Xu)	DOWCO07F
Octanol and air contained in gas-tight syringe	Partition coefficient n-octanol/air (log value)	Log Koa 4.22 at 24°C	Octanol and air contained in gas-tight syringe with a valve. ^{14}C-D4 dissolved into octanol and distribution determined between the two phases by using an HPLC equipped with a radiomatic detector. Air samples analyzed by liquid scintillation analyzer.	6	1	Dow Corning Corporation 2006a (Study Director: Xu)	DOWCO06A
3-phase equilibrium method	Partition coefficients: air/water, octanol/air, and octanol/water	At temp. of 21.7 ºC: K_{AW} = 2.69; K_{OA} = 4.29; K_{OW} = 6.98	Simultaneous determination of three partition coefficients with same quantitation method for all media.	6	2	Xu and Kropscott 2012	XU12A

[1] Physical-chemical property studies include a range of possible scores between 6 and 24. A higher score indicates a lower reliability. Blue color indicates high reliability; no color indicates scoring not applicable.

3.3 Environmental Fate Properties

3.3.1 Hydrolysis

A preliminary study was conducted (Dow Corning Corporation 2004) (following OECD Guideline 111 (Hydrolysis as a function of pH) to determine appropriate methods for investigating hydrolysis of D4, considering its volatility. The investigation used both two-piece reaction vessels and sealed tubes, and different conditions (vial type, medium) were investigated. In the two-piece system, a half-life of 3.5 days at pH 7 (25°C) was determined, although recovery decreased over time. In the sealed tubes, the half-life was 91 hours (equivalent to 3.8 days) at pH 7 and 33 hours (equivalent to 1.4 days) at pH 9 (25°C). The study determined that the sealed tube method was more effective and this approach was used in the full study (Dow Corning Corporation 2005) which was also conducted following OECD Guideline 111 but under GLP. The full study was conducted at pH 4, 7, and 9 and temperatures of 10, 25, and 35°C. Half-life values ranged from 12 minutes (equivalent to 0.008 days) for pH 9 at 35°C to 23 days for pH 7 at 10°C. The average half-life for pH 7 at 25°C was 80 hours (3.3 days), in good agreement with previously reported preliminary results. For pH 7.0 at 12°C, a relevant condition for risk assessment purposes for fresh water, the predicted value of the half-life is 16. 7 days. For pH 8.0 at 9°C, a condition relevant for marine water, the predicted half-life is 2.9 days.

Information on the hydrolysis of D4 is provided in Table 3-2, with the corresponding reviews in Appendix B.

Table 3-2. Hydrolysis

Method	Property	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from CSR)	Reference	Reference ID
Two-piece and sealed single-piece vessel reactions; OECD Guideline 111	Hydrolysis	Half-life of 3.5 days at pH 7 and 25°C in the two-piece vessels though decreasing recoveries occurred. Sealed tube experiments had half-life of 91 hours (equivalent to 3.8 days) at pH 7 and 33 hours (equivalent to 1.4 days) at pH 9 (25°C).	Preliminary study factored into the experimental design many of the challenges associated with testing a volatile compound. Precautions were taken to account for variability and additional factors that could lead to experimental error. Results demonstrated feasibility of sealed tube approach for the full study.	17	1	Dow Corning Corporation 2004 (Study Directors: Durham and Kozerski)	DOWCO04A
OECD Guideline 111	Hydrolysis	Half-life values ranged from 12 minutes (equivalent to 0.008 days) at pH 9, 35°C, to 23 days for pH 7 at 10°C. The average half-life for pH 7 at 25°C was 80 hours (3.3 days), in good agreement with previously reported preliminary results. For pH 7.0 at 12°C, a relevant condition for risk assessment purposes for fresh water, the predicted value of the half-life is 16. 7 days. For pH 8.0 at 9°C, a condition relevant for marine water, the predicted half-life is 2.9 days.	Guideline study conducted under GLP with well-documented findings. To eliminate losses of D4 from the test, the methodology uses one-piece, hermetically sealed glass reaction vessels.	15 Reviewed by Bridges and Solomon (BRIDG16A) and scored 3.7 for methods and 4 for relevance	1	Dow Corning Corporation 2005 (Study Director: Durham)	DOWCO05A

[1] Hydrolysis studies include a range of possible scores between 14 and 56. A higher score indicates a lower reliability. Blue color indicates high reliability.

3.3.2 Phototransformation

D4 in the atmosphere is not expected to undergo direct photolysis, but should undergo indirect photolytic degradation through hydroxyl radical (OH) oxidation. The nitrate (NO_3) radical and ozone (O_3) react with D4 at much slower rates, although a high level of O_3 and water may accelerate the reaction of D4 with OH (Abe et al., 1981). Reaction rate constants with the OH at 25 ºC range from 0.95 to 2.34 × 10^{-12} $cm^3molecule^{-1}s^{-1}$ (Bernard et al. 2018; Kim and Xu 2017; Safron et al. 2015; Sommerlade et al. 1993; Atkinson 1991; Xiao et al. 2015). Based on an average tropospheric hydroxyl radical concentration of approximately 10^6 molecules/cm^3 (Stone et al. 2012), this equates to a half-life of approximately 4.5 to 13 days. Another study (Dow Corning Corporation 1980) reported an atmospheric half-life of 0.3-0.5 days in a Teflon-lined chamber and 1.1 days in glass chamber; however, this study did not provide rate constants.

D4 is also expected to sorb to particulate matter present in the atmosphere. Lab experiments conducted with single aerosol types found that D4 rapidly (e.g., within minutes) sorbs to aerosol particles (Kim et al. 2016; Navea 2009a,c). For many aerosol types, D4 irreversibly binds to the aerosol such that desorption does not completely occur (Kim et al. 2016) mostly due to the transformation of D4 on the aerosol surface. Relative humidity was found to have a large impact on D4 sorption to aerosols and its transformation on the surface. Since the experiments were largely conducted at very low relative humidities (≤ 30% relative humidity), translation of the measured sorption kinetics into environmental relevant conditions is difficult. Navea (2009a) modeled a half-life of 8.75 days at 60% relative humidity for D4 in the presence of an aerosol surface concentration of 1.1x10^{-3} m^2/m^3.

In air, it is also well established that D4, D5 and D6 readily degrade by interaction with OH radicals (Atkinson 1991, Latimer et al. 1998, Sommerlade et al. 1993). D4, D5 and D6 are mainly released from the urban centers where the OH radical concentrations are much higher than the global average OH radical concentration used to estimate their current half-lives (Suzuki et al. 1984; Nunnermacker et al. 1998; Dillon et al. 2002; Ren et al. 2002; 2003; Hjorth et al. 1984; Schade et al. 2002). Very recent work using actual monitoring data demonstrates the real-life degradation of D4, D5 and D6 in air may be much faster than what is currently estimated (Xu et al. 2019). The authors have demonstrated that D4, D5 and D6 may be

transported much shorter distances in the real atmosphere than estimated using models based on the OH radical mechanism. In addition, the data suggest that the spatial patterns of the D4, D5 and D6 concentration ratios cannot be explained by OH radical mechanism alone, suggesting that additional degradation mechanism(s) are operative in the atmosphere for these compounds. This work suggests that the real-life half-life may be much shorter (~2 days) than the experimentally determined half-life. A collaborative effort with experts from Norway, Stockholm University, and the University of Toronto is underway to better determine the atmospheric half-lives of D4, D5 and D6 using field data from two south-to-north transects, and selected specific locations that reflect the effects of air circulation patterns both in Europe and North America. Completion of the project is expected by the end of 2020.

Information on phototransformation is provided in Table 3-3, with the corresponding reviews in Appendix B.

Table 3-3. Phototransformation

Method	Results	Remarks	Evaluation (score based on template)[1]	Klimisch score (from CSR unless noted)	Reference	Reference ID
Other (measured)	Rate constants for OH radical at 295K is 1.12 x 10^{12} $cm^3molecule^{-1}s^{-1}$. Replicates are in excellent agreement and overall uncertainty in this rate constant is 13%.	Atmospheric half-life of 13 days assuming an OH radical concentration of 10^6 mol/cm^3.	27	N/A	Bernard et al. 2018	BERNA18A
Other (measured)	Rate constant for OH radical at 298 K: 0.95±0.18 ×10^{-12} $cm^3molecule^{-1}s^{-1}$	Atmospheric half- life approx. 11.5 days assuming global average OH concentration of 1.5*10^6 mol/cm^3.	25	N/A	Kim and Xu 2017	KIM17A; KIM17B (SI[2])
Other (measured)	Rate constant for OH radical at 298 K = 2.34 x10^{-12} $cm^3molecule^{-1}s^{-1}$.	Atmospheric half-life approx. 4.5 days assuming global average OH concentration of 7.7 x10^5 $molecules/cm^3$	27	N/A	Xiao et al. 2015	XIAO15A
Other (measured)	Rate constant for OH radical at 298 K = 1.9 x 10^{-12} $cm^3molecule^{-1}s^{-1}$. Rate constant for OH radical at 255 K = 1.45 x 10^{-12} $cm^3molecule^{-1}s^{-1}$.	Estimated tropospheric half-life of 8 days at 255 K (average tropospheric temperature) assuming average OH radical concentration of 10^6 molecules/cm3	29	N/A	Safron et al. 2015	SAFRO15A
Other (measured)	Rate constant for OH radical at 297 K = 1.26 x $10^{-12}$$cm^3molecule^{-1}s^{-1}$.		29	2	Sommerlade et al. 1993	SOMMER93A
Other (measured)	Rate constant for OH radical at 297 K = 1.01 x 10^{-12} $cm^3molecule^{-1}s^{-1}$. Little reaction with NO_3 or O_3		30	4 (note: K2, Key study, in ECHA)	Atkinson 1991	ATKIN91A
Other (measured)	Rate constant for OH radical at 300K = 3.08×10^{-12} cm3/s. [Note that units do not include $molecule^{-1}$.] No reaction with N2, O2, or H2O.		34	4	Bayer 1990 (Study Director: Parlar, H.)	BAYER90A
Other (measured)	The reaction of D4 with hydroxyl radicals was found to be accelerated by the presence of high conc. of ozone (>0.4 mol/l) and water vapour.	Relative half-life (compared to n-octane) with O3 at ~10^{-3} mol/L is 3.3 days. Note that actual atmospheric O3 concentrations are ~ 10^{-9} mol/L	33	4	Abe et al. 1981	ABE81A
Other (measured)	Specific pseudo first-order rate constants not reported. Nitric acid, nitroethane, or nitrogen dioxide present to produce OH radicals	Atmospheric half-life: 0.3-0.5 days in Teflon-lined chamber and 1.1 days in glass chamber	33	4	Dow Corning Corporation 1980 (Study Director: Lane, T.H.)	DOWCO80A

Method	Results	Remarks	Evaluation (score based on template)[1]	Klimisch score (from CSR unless noted)	Reference	Reference ID
Modeling	Modeling exercise using rates measured by Navea et al. 2009a, Atkinson 1991 and Sommerlade et al. 1993 is contained in the second half of this report. (The first half describes the laboratory investigation of Navea et al. 2009a).	Half-life of 9.21 days with OH radical concentration of 10^6 molecule/m^3. Half-life of 7.4 days when accounting for diurnal changes in D4 and OH radical concentrations in July (full sun). Half-lives ranging from 7.69 days (20% humidity) to 8.75 days (60% humidity) when an aerosol surface concentration of $1.1x10^{-3}$ m^2/m^3 is included in the model.	NA	N/A	Navea et al. 2009b	NAVEA09B
Other (measured)	Rate constant for reaction with particulate matter and O3 is $1.8*10^{10}$ /cm^2*s (cm^2 is surface area of particulate matter) at 40% relative humidity.	Atmospheric oxidants such as ozone may modify the mineral dust surface such that uptake of D4 by mineral dust may be important. O3 enhances D4 uptake and may cause polymerization reaction of D4.	29	N/A	Navea et al. 2009a	NAVEA09A
Other (measured)	Sorption and desorption rates and isotherms for 9 different aerosol types. Aerosol-air partition coefficients ranged from 0.09 to 50.4 L/m^2 for D4. Carbon black and kaolinite showed the largest sorption density; sea salt was the lowest. D4 sorbed quickly into aerosols reaching equilibrium within 2 hours.	Experiments were conducted at 30% relative humidity (daytime desert conditions). Relative humidity significantly impacts sorption and thus it is difficult to extrapolate these experiments to true environmental conditions.	26	N/A	Kim and Xu 2016	KIM16A
Other (data analysis of published data)	D4 and D6 concentrations were correlated with measured concentrations for D5 at the same times and locations in the majority of the datasets. as the sampling sites changed from the source to remote locations along a south to north transect, average cVMS concentrations in air decreased in an exponential manner.	700 measurements of outdoor air concentrations were taken from peer-reviewed journals and government reports between 2004 and 2016 with the latitudes of the sampling sites ≥35ºN. Air monitoring data from immediate point sources such as manufacture sites, waste water treatment plants and landfills were excluded to avoid bias.	18	NA	Xu et al. 2019	XU19A
Other (measured)	D4 can be removed from the gas phase by reaction with components of mineral dust aerosol and carbon black under dry (≤ 1% relative humidity conditions).	Paper not useful since only deals with sorption of D4 to particulate matter. Difficult to translate to realistic environmental conditions.	31	N/A	Navea et al. 2009c	NAVEA09C

[1] These studies include a range of possible scores between 15 and 60. A higher score indicates a lower reliability. Blue color indicates high reliability; yellow color indicates medium reliability; no color indicates scoring not applicable.

[2] Peer-reviewed articles with a supplemental information (SI) that was reviewed are noted. The SI is documented as a separate document (e.g., KIM16A is main document and KIM16B is the SI). SI's are not listed in the references.

3.3.3 Biodegradation

D4 showed little biodegradation (3.7%) under the conditions of an OECD 310 29-day sealed headspace test (Springborn 2005). This is considered a screening test for ready biodegradability. The test substance was not toxic to the inoculum (which was demonstrated to be acceptable) and the reference control performed as expected. In a study conducted following the Bourquin microcosm test (EPA 660/3-75-035) modified to accommodate a volatile test substance (Springborn 1991d), losses of D4 from the sediment-water system were observed in both active and sterile control chambers. Losses were likely due to hydrolysis or absorbed compound from backflow. Biodegradation was not observed. However, since mass balance in this study was variable, and the mean recovery values were below 80%, the reliability of this study is downgraded.

Aerobic and anaerobic transformation in water/sediment systems was investigated in a preliminary study with sediment from Sanford Lake, Michigan (Dow Corning Corporation 2008c) and then in full studies with sediment from Lake Pepin, Wisconsin (Dow Corning Corporation 2009a,b). These latter studies gave half-lives of 365 days (anaerobic conditions) and 242 days (aerobic conditions) and indicated that hydrolysis was likely responsible for losses of D4 in the systems. Complete mineralization of D4 or its hydrolysis products was very slow in both systems, and methanogenesis in the anaerobic study was minimal.

Degradation in soil was studied in open and closed tubes to examine the competing processes of volatilization and hydrolysis over a range of relative humidity (Xu and Chandra 1999). Two soil types were used, with one more highly weathered (Wahiawa soil). Half-lives for degradation in soil were 0.04, 0.08, and 0.89 days for Wahiawa soil at relative humidity of 32, 92, and 100%, respectively, and 3.54 and 5.25 days for Londo soil at relative humidity of 32 and 92%, respectively. At high humidity, degradation slowed and volatilization became predominant. Both processes act to reduce persistence of D4 in soils. The pathways of degradation were investigated in the Wahiawa soil in closed tubes (Xu 1999) and shown to follow a step-wise process beginning with ring-opening hydrolysis to form linear oligomeric siloxane diols,

followed by further hydrolysis to form monomer dimethylsilanediol. Data from these two publications were used in a calculation to estimate the degradation rate in an “average” soil (Dow Corning Corporation 2007a). These calculations provided a half-life for D4 in a temperate soil of 4.1–5.27 days (at relative humidity 50–90%) and, for a tropical soil, 0.046–0.078 days (at relative humidity 50–90%).

In summary, D4 degradation in water, sediment, and soil appears to occur primarily by abiotic processes, as little biodegradation has been observed in laboratory studies (e.g., 3.7% in OECD 310). Degradation in water is largely by hydrolysis. In a standard laboratory study, the half-life in sediment was 365 days under aerobic conditions and 242 days under anaerobic conditions. In soil, dissipation occurs through both volatilization and hydrolysis, with a measured half-life of 0.04 days to 5.25 days across different soil types. At high humidity, degradation slowed and volatilization became predominant. Due to volatilization and hydrolysis, D4 is not persistent in water and air. However, once incorporated into sediment, degradation appears to be slow. It should be noted that these degradation rates have been derived from laboratory studies. Recent research has suggested that degradation processes under real environmental conditions may be different. For example, it has been found that the capacity of some sediment-feeding organisms to metabolize hydrophobic organic contaminants may exceed that of microbial degradation. In addition, interactions between microbes and eukaryotes enhance microbial activity, which may further increase microbial degradation compared to what is measured in standard laboratory tests. (Selck and Forbes 2018).

Information on biodegradation of D4 is provided in Table 3-4, with the corresponding reviews in Appendix B.

Table 3-4. Biodegradation

Method	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from CSR unless noted)	Reference	Reference ID
OECD 310 - sealed vessel CO_2 evolution (screening test for ready biodegradability)	Activated sludge inoculum added to aqueous medium. Little biodegradation observed (3.7% of theoretical at day 29).	Guideline study conducted under GLP with well-documented findings. The test substance was not toxic to the inoculum (which was demonstrated to be acceptable) and the reference control performed as expected.	21 (possible score 18–72) Reviewed by Bridges and Solomon (BRDIG16A) and scored 3.4 for methods, 2.0 for relevance.	1	Springborn 2005 (Study Director: Gledhill)	SPRIN05B
Bourquin microcosm	Biodegradation not observed. Losses of D4 likely due to hydrolysis or issues with backflow into traps.	Chambers containing sediment and water were modified to address D4 volatility. Mass balance was variable, and recovery value were below 80%. Study used the Bourquin microcosm test (EPA 660/3-75-035) modified to accommodate a volatile test substance.	29 (possible score 17–68) Reviewed by Bridges and Solomon (BRDIG16A) and scored 3.4 for methods, 2.75 for relevance. Method score reduced to 1.7 due to poor recovery	1	Springborn 1991d (Study Director: Fackler)	SPRIN91D
OECD 308 – Aerobic transformation in water/sediment systems	In 22 days, about 32% of the D4 underwent hydrolysis in the sediment from Sanford Lake, MI. Calculated half-life of 47 days. Complete mineralization of D4 or hydrolysis products not significant.	This is an interim report of preliminary results.	35 (possible score 17–68) Reviewed by Bridges and Solomon (BRDIG16A) and scored 2.6 for methods, 3.75 for relevance.	2	Dow Corning Corporation 2008c (Study Directors: Xu and Miller)	DOWCO08C
OECD 308 – Aerobic transformation in water/sediment systems	Aerobic half-life in Lake Pepin, WI sediment was 242 days. Hydrolysis indicated. Complete mineralization of D4 or hydrolysis products very slow.	Guideline study conducted under GLP with well-documented findings.	20 (possible score 17–68)	2	Dow Corning Corporation 2009a (Study Director: Xu)	DOWCO09A
OECD 308 – Anaerobic transformation in water/sediment systems	Anaerobic half-life in Lake Pepin, WI sediment was 365 days. Hydrolysis indicated. Complete mineralization of D4 or hydrolysis products very slow. Methanogenesis not significant.	Guideline study conducted under GLP with well-documented findings.	20 (possible score 17–68) Reviewed by Bridges and Solomon (BRDIG16A) and scored 3.5 for methods, 3.5 for relevance.	2	Dow Corning Corporation 2009b (Study Director: Xu)	DOWCO09B

Method	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from CSR unless noted)	Reference	Reference ID
Two soil types in open and closed tubes	For closed tubes, half-lives for degradation in soil were 0.04, 0.08 and 0.89 days for weathered Wahiawa soil at relative humidity of 32, 92 and 100%, respectively and 3.54 and 5.25 days for Londo soil at relative humidity of 32 and 92%, respectively. At high relative humidity, degradation slowed and volatilization became predominant for open tubes.	Publication on rates of degradation and volatilization in soils. Two soil types were used, with one more highly weathered (Wahiawa soil).	18 (possible score 15–60)	2	Xu and Chandra 1999	XU99B
One soil type in closed tubes	Degradation steps include ring-opening hydrolysis to form linear oligomeric siloxane diols, followed by further hydrolysis to form monomer dimethylsilanediol.	Publication on degradation pathway in Wahiawa soil	13 (possible score 11–44)	2	Xu 1999	XU99A
Extrapolation of existing data	Half-life in a temperate soil is 4.1–5.27 days (relative humidity 50–90%). In a tropical soil this would be 0.046–0.078 days (relative humidity 50–90%).	Report presenting calculation of degradation rates for an “average” soil based on data in XU99A and XU99B.	Not scored	2	Dow Corning Corporation 2007a (Study Director: Xu)	DOWCO07A

[1] The range of possible scores is provided. A higher score indicates a lower reliability. Blue color indicates high reliability, yellow color indicates medium reliability, and no color indicates scoring not applicable.

Two studies listed as Klimisch 4 in the CSR are not included above (Wolfgang and Rast 1995 and Dow Corning 1976). More recent and reliable data are available to assess biodegradability without these studies.

3.3.4 Soil Adsorption and Desorption

The adsorption/desorption behavior of D4 was studied using OECD TG 106 (Adsorption - Desorption Using a Batch Equilibrium Method) (Dow Corning Corporation 2007b). Sorption of ^{13}C-D4 by three different soils varying in organic carbon content, pH, and texture was studied over a range of concentrations. The range of the log of the organic carbon/water partition coefficient (Koc) for absorption was 4.17 to 4.27 with an overall average of 4.22. For desorption, Koc ranged from 4.23 to 4.39, with an average of 4.30. The results indicate that D4 has a strong affinity to sorb to soil. The linear isotherms and the general agreement in the log Koc values across the different soils suggested that partitioning into soil organic matter dominated the overall sorption of D4 from water. The comparable values of log Koc for adsorption and desorption indicated that the sorption of ^{13}C-D4 was largely reversible for short contact times (ca. 48 h). Kozerski et al. (2014) summarized these results and concluded further that compared to traditional hydrophobic organic compounds, Koc values for cVMSs are significantly lower than expected based on Kow. A linear free energy relationship analysis showed that these differences could be rationalized quantitatively in terms of the inherent characteristics of cVMSs, combined with the differences in solvation properties of organic matter and octanol. Panagopoulos et al. (2015) reported the log K_{OC} for D4 as 5.06 in a study conducted in a closed system using sediment as the organic carbon source and a purge and trap equilibrium method. The indirect assessment approach used in this study is less reliable than the guideline study described above (Dow Corning Corporation 2007f).

Information on soil sorption and desorption is provided in Table 3-5, with the corresponding reviews in Appendix B.

Table 3-5. Soil adsorption and desorption.

Method	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from CSR unless noted)	Reference	Reference ID
OECD 106, Adsorption-desorption using batch equilibrium	In three soils, range of log Koc for absorption was 4.17–4.27 with overall average of 4.22. For desorption, 4.23–4.39, with average of 4.30.	Guideline study conducted under GLP with well-documented findings. The results indicate that D4 has strong affinity to sorb to soil. The linear isotherms and the general agreement in the log Koc values across the different soils suggested that partitioning into soil organic matter dominated the overall sorption of D4 from water. The comparable values of log Koc for adsorption and desorption indicated that the sorption of ^{13}C-D4 was largely reversible for short contact times (ca. 48 h).	19 (possible score 17–68)	1	Dow Corning Corporation 2007b (Study Director: Miller)	DOWCO07B
		Published article summarizing DOWCO07B.	Not scored		Kozerski et al. 2014	KOZER14A
Purge and trap method; Sediments varying in organic carbon content, pH, and texture were studied over a range of concentrations.	Sediment based log Koc for D4 is 5.06 and log Kd_{oc} is 5.05	Publication describes measurements made using sediment as the organic carbon source, which could account for difference in log Koc compared to other studies. Indirect method used, less reliable than guideline methods.	13 (possible score 6-24)	NA	Panagopoulos et al. 2015	PANAG15A

[1] The range of possible scores is provided. A higher score indicates a lower reliability. Blue color indicates high reliability, no color indicates scoring not applicable.

3.3.5 Bioaccumulation

A number of studies published since 2008 were found covering D4 bioaccumulation metrics, some of which were computer modeling estimates, laboratory studies, and field studies. These studies are reviewed and summarized herein. Terminology used in this section includes bioconcentration factor (BCF), biomagnification factor (BMF), trophic magnification factor (TMF), and biota sediment accumulation factor (BSAF). Bioconcentration is the intake and retention of a compound through respiration of water or air[4]. Biomagnification (or trophic magnification) refers to what occurs when a compound moves up the food chain to higher trophic levels and exceeds the equilibrium concentration found between an organism and its environment.[5] Bioaccumulation is chemical intake by an organism through all means: contact, respiration, and ingestion.[6] BSAF is defined as the lipid-normalized concentration of an organic chemical with hydrophobic properties in an organism relative to the organic carbon-normalized concentration of the organic chemical in the sediment in which the organism was exposed.[7]

As cited individually below, bioaccumulation related information is provided in Table 3-6 through Table 3-10.

3.3.5.1 Modeling of bioaccumulation

Computer-based modeling tools are widely used to estimate chemical processes of bioaccumulation (i.e., BCF, BMF, etc.) and are largely based on the physical-chemical properties (e.g., lipophilicity, metabolism rate) of the compound in question. Review publications such as by Nichols et al. (2007) have examined the use of computer modeling of chemical absorption, distribution, metabolism, and excretion (ADME) data in assessing bioaccumulation processes in fish. As detailed in the European OECD Test 305 Guideline – Bioconcentration in Fish[8], kinetic bioconcentration factors (BCF_k) are commonly derived from a

[4] Accessed on February 21, 2019 at https://link.springer.com/referenceworkentry/10.1007%2F1-4020-4494-1_31

[5] Accessed on February 21, 2019 at https://link.springer.com/referenceworkentry/10.1007%2F1-4020-4494-1_31

[6] Accessed on February 21, 2019 at https://link.springer.com/referenceworkentry/10.1007%2F1-4020-4494-1_31

[7] Accessed on February 21, 2019 at https://bsaf.el.erdc.dren.mil/about.cfm

[8] Accessed on October 1, 2019 at https://www.oecd.org/env/test-no-305-bioaccum ulation-in-fish-aqueous-and-dietary-exposure-9789264185296-en.htm

simple, first-order, one-compartment fish model for use in federal regulatory action. However, the one-compartment toxicokinetic model that has been in long-term use in such guidelines is not consistent with the current state of the science, experimental practices, and information needs for bioaccumulation and risk assessment, and proposed new methods are detailed by Gobas et al. (2019) and Gobas and Lee (2019). In addition, metabolism is a key process potentially attenuating bioaccumulation of chemicals in aquatic organisms and may strongly affect internal concentrations of parent compounds and metabolites (Ashauer et al. 2012). Metabolic studies on D4 have been undertaken with fish by Domoradzki et al. (2017a) and Cantu and Gobas (2019) and benthic invertebrate species (Selck et al. 2019); the compound has been found to be highly metabolizable, with metabolism rate constants (k_M) that influence bioaccumulation of the compound in aquatic organisms. The fish k_M values with rainbow trout have been used with other available bioaccumulation parameters to calculate BCF and BMF values for D4 using the newest bioaccumulation modeling method (Gobas et al. 2019), as seen in Table 3-6.

Table 3-6. Calculated BCF and BMF values for D4 derived for rainbow trout using measured input parameters and the Fish Bioaccumulation ADME Calculator for OECD 305 Dietary Bioaccumulation Tests in Fish: Excel Model Version 1.1 from Gobas et al. (2019).

Endpoint	Units	Value
BCF_k	L/kg fish ww	2953
BCF_{kL}	L/kg fish ww	3567
BMF_k	kg food dw/kg fish ww	0.068
BMF_{kL}	kg lipid/kg lipid (or unitless)	0.3611

BCF_k is the ratio of the concentration in fish body (wet wt) to the concentration in water (in units of L/kg fish ww). BCF_{kL} is the BCF_k converted to a BCF_{kL} for a standard fish with a lipid content of 5% (in units of L/kg ww). BMF is the ratio of concentration in fish body (wet wt) to concentration in food (dry wt) (in units of kg food dw/kg fish wet wt). BMF_{kL} is the ratio of the concentration in fish body (lipid wt) to concentration in food (lipid wt) (in units of kg lipid/kg lipid, or unitless).

3.3.5.2 Laboratory Studies

Xue et al. (2018) presents information on bioaccumulation in the common carp using both laboratory exposures and a trophic level study on numerous organisms collected from an estuary. The reported BCF value for carp was 6,197 L/kg (Xue et al. 2018; Table 3-10). However, the kinetic parameter model fit to the data from Xue et al. (2018) could not be reproduced by Kim et al. (2019), and Xue et al. (2018) also erred in reporting dry weight fish concentration data, not wet weight concentrations as are usually done for kinetic modeling of BCF. Kim et al. (2019) reanalyzed the data, and estimated values of K_1 (uptake rate) and k_2 (elimination rate) by optimizing the parameters using the OECD 305 Guideline methods and computer modeling of uptake and elimination fish and water data (via Berkeley Madonna software[9]). Since dry weight fish concentrations were reported and no water content (or solid content) of the fish was noted by Xue et al. (2018), a water content of 70% (or 30% of solid content) was assumed. The results of optimized parameters from the new regression calculated by Kim et al. (2019) are shown in Table 3-7 and the improved fit of the revised kinetic parameters versus Xue et al. (2018) is shown graphically in Figure 3-1. The new values of K_1 and k_2 are different from those of Xue et al. (2018) and the revised D4 BCF_k value with the common carp is 1673 L/kg. This D4 carp BCF_k value of 1673 L/kg is two-fold less than the modeled D4 BCF_{kL} of ~3600 L/kg ww (see Table 3-6).

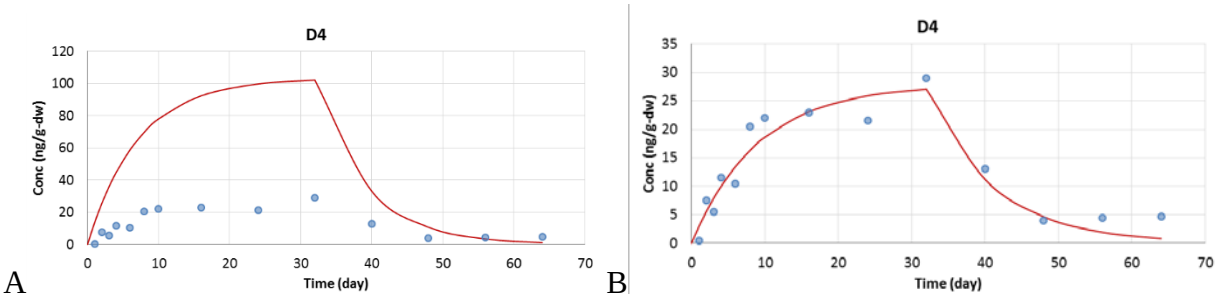
[9] Berkeley Madonna: Modeling and Analysis of Dynamic Systems Version 8.3.18, https://berkeley-madonna.myshopify.com/

Table 3-7. Bioconcentration kinetic parameters from Xue et al. (2018) compared to values fit by Kim et al. (2019) using the OECD 305 Guideline one-box model and Berkeley Madonna software.

Parameter	Units	Value reported by Xue et al. (2018)	Modeled Value by Author (2019)[a]
K_1 (Uptake)	L kg-ww^{-1} day^{-1}	872	184
k_2 (Elimination)	day^{-1}	0.1407	0.11
BCF_k (K_1/k_2)	L kg-ww^{-1}	6197	1673

[a] Modeled using OECD 305 one-box model and Berkeley Madonna software.

Figure 3-1. (A) Fit of D4 kinetic parameters modeled by Xue et al. (2018) and (B) the revised modeling by Kim et al. (2019). The kinetic parameters employed in this analysis are shown in Table 3-7, along with resulting BCF_k values.



It is generally considered problematic to assign a BMF value to a material based solely on field data, due to factors such as unknown diet selection, movement/migration, and varying chemical exposure concentrations in water and sediment. Xue et al. (2018) reported a D4 BMF of 3.2 going from plankton (trophic level or TL 2.14) to Japanese snapping shrimp (TL 2.59) using Eq. 10 in Xue et al. (2018). This BMF value could not be completely reproduced by Kim et al. (2019), as shown in Table 3-8. The revised D4 BMF value from the plankton-shrimp relationship was lower at 2.6 compared to the original value of 3.2.

Table 3-8. Biota concentration data and BMF values from Xue et al. (2018) and new BMF recalculated by Kim et al (2019).

Species	Trophic Level	D4 Conc. (ng/g-lw)
Japanese snapping shrimp	2.59	750
Plankton	2.14	239
BMF		
Xue et al. (2018)		3.2
New calculation		2.6

The D4 BMF study of Xue et al. (2018) is considered less reliable than studies conducted under OECD 305 guidelines, such as the D4 laboratory BMF study by Woodburn et al. (2013) in which rainbow trout (*Oncorhynchus mykiss)* were directly exposed to ^{14}C-labeled D4 through the diet over 77 days. This study determined an half-life of approximately 20 days for D4 and BMF and lipid adjusted BMF (BMF_L) values of 0.28 and 0.66 for D4, respectively (Woodburn et al. 2013; Table 3-10); the latter lipid-adjusted value is comparable to the modeled D4 BMF_{kL} value of 0.36 (Table 3-6).

3.3.5.3 Field Studies

TMFs are useful measures of trophic magnification and represent the diet-weighted average BMF of chemical residues across food webs. As such, TMFs are commonly used for the assessment of chemical bioaccumulation in food webs, as they are derived from field measurements thereby providing information on the actual behavior of the chemical in the environment. The TMF value is typically derived from the slope of a log-normal regression of chemical residues in organisms (lipid-normalized) upon their corresponding trophic levels. As field measurements, TMFs can provide valuable insights into the real-world bioaccumulation behavior of chemicals; they have been referred to as the "gold standard" of bioaccumulation metrics (Gobas et al. 2009). However, like all bioaccumulation metrics, TMFs may be subject to a degree of uncertainty as a consequence of systematic sampling bias, spatially-variable concentrations in water and sediments, and variations in biotransformation rates (Conder et al. 2012; Burkhard et al. 2012).

Trophic magnification factors (TMFs) are generally calculated as the slope b by the concentrations of lipid normalized ([chemical concentration]$_{lw}$) regressed against the trophic level (TL) position (Kidd et al. 2019); the food web TMF value is the antilog of the slope:

$$\log[\text{chemical concentration}]_{lw} = a + bTL \quad (1)$$

$$TMF = 10^{b} \quad (2)$$

Numerous field studies have been conducted to better understand biota/sediment BSAF and food web TMF values for the cVMS materials (D4, D5, and D6). For example, Dow Corning Corporation conducted a field study that measured D4 and other cVMSs (D5 and D6) in the food web and sediments of a temperate lake (Lake Pepin) in Minnesota USA (Dow Corning Corporation 2009c). They measured these cVMSs in two benthic macroinvertebrate species and 15 fish species from different trophic levels and found that concentrations of D4 decrease with increasing trophic level, providing evidence that D4 does not biomagnify but biodilutes (Dow Corning Corporation 2009c). Dow Corning Corporation conducted another field study in an Ontario lake (Lake Opeongo) that assessed cVMSs in lake sediment, zooplankton, and fish tissue samples from different trophic levels. Concentrations of D4 ranged from 0.87 to 3.77 ng/g ww in fish tissues and were 0.43 ng/g ww om zooplankton; however, cVMS contamination was found in all reagent blanks, and the data, therefore, are not considered reliable (Dow Corning Corporation 2010a). Another study by Dow on the food webs of the inner and outer Oslofjord, Norway characterized sediment and biological tissue and found the D4 TMFs was between 0.2 to 0.6 (Dow Corning Corporation 2010b). The study determined that D4 does not biomagnify in this marine food web, similar to the field study conducted in 2009 on the Lake Pepin trophic system (Dow Corning Corporation 2009c). Another study by Dow used data collected on the food web of Lake Champlain and a biouptake model to explore confounding factors that may contribute to uncertainties in TMF (Powell et al., 2014). The authors reported that reliable TMFs could not be obtained for cVMS in the aquatic food web of Lake Champlain due to the experimental design, concentration gradients, and species migration across the study area. In addition, modelling results indicated that because cVMS is biotransformed in biota, concentration gradients couple with experimental design can cause apparent TMFs to be both

greater than or less than 1, depending on the magnitude of the concentrations gradients in the environment and species migration.

Borgå et al. (2012) and Kierkegaard et al. (2011, 2013) used a purge and trap extraction method developed by these researchers that was subsequently found to be unreliable for cVMS determinations in a review paper that characterized reliability of D4 studies (Bridges and Solomon 2016) and this should be used with caution. The extraction method was refined and presented in Borgå et al. (2013) and those data show that D4 concentrations in the pelagic food webs in three Norwegian lakes (two lakes were human influenced and one lake was remote) were low, often below the limit of quantification (LOQ) and a low TMF of 0.7 (0.5-0.9) was determined, suggesting biodilution of D4.

McGoldrick et al. (2014a) characterized biological samples from various food web compartments in Lake Erie, Canada to determine TMF values for cVMS materials. D4 concentrations in biota included plankton = 2 ng/g (below limit of detection), mayfly = 7 ng/g, and fish = 9-13 ng/g. Observed TMFs were assessed in various food web configurations to investigate the effects of food web structure. The cVMS TMF estimates were highly dependent on the inclusion/exclusion of the organisms occupying the highest and lowest trophic levels and were <1 for D4 (indicating trophic dilution) in four of the five food web configurations investigated and when the highest and lowest trophic levels were excluded (walleye and plankton), the TMF value was 1.1 for D4. Overall, TMF <1 were observed for D4 in 4 of 5 food web configurations. When all species data are considered, the average D4 TMF = 0.74 and when all data are considered (excluding plankton), the D4 TMF = 0.73.

Hong et al. (2014) presents a one-time sampling event in Dalian China in the Chinese Sea which characterized marine sediment, seawater, fish tissue, and effluent from municipal waste streams to understand the baseline concentrations of cVMSs. Hong et al. (2014) found mean concentrations of total methyl siloxanes were 46.1 ± 27.2 ng/L in seawater, 12.4 ± 5.39 ng/g dry weight (dw) in sediment, and 5.10 ± 1.34 wet weight (ww) in fish. The mean value of the BSAF was 0.716 ± 0.456 for D4 (Hong et al. 2014).

Jia et al. (2015) examined cVMS behavior in a coastal marine food web in Dalian Bay in northern China. The authors reported on a zooplankton-invertebrate-fish aquatic food web and trophic magnification was not statistically significant for D_4 (correlation coefficient or $R^2 = 0.02$, $p = 0.16$). These aquatic data indicate that neither trophic magnification nor trophic dilution was occurring with D4 in this aquatic food web.

Krogseth et al. (2017) used GC/MS to measure cVMS concentrations in benthic fauna, sticklebacks (fish), brown trout, and char in Lake Storvannet, a subarctic lake in Norway. The measured biota concentrations of all cVMS, including D4, indicated that none of the cVMS materials (D4, D5, D6) exhibited trophic biomagnification; the measured D4 TMF in Lake Storvannet was <1, indicating trophic dilution. The BSAF for D4 in sticklebacks averaged 1.5, with a range of 0.5-3.3, for char the BSAF was <6.2, and the BSAF was non-detect in trout.

Powell et al. (2017) examined cVMS concentrations in a pelagic marine food web in Tokyo Bay, Japan. The authors found no evidence of trophic magnification with D4 in the studied species and found no statistically significant association between lipid-adjusted concentrations and trophic level for D_4 (correlation coefficient or $R^2 = 0.04$, $p = 0.52$). Using bootstrap analysis, the authors calculated that the probability that the D4 TMF >1 in the Tokyo Bay food web was less than 0.1%.

Bridges and Solomon (2016) conducted a QWoE evaluation on the persistence, bioaccumulation, and ecotoxicity of cVMS chemicals. The authors examined all available BCF, BMF, and TMF data on D4 and concluded that studies in natural food webs "*support a conclusion that the cVMSs do not biomagnify, a conclusion that is consistent with results of toxicokinetic studies*".

The field data of Xue et al. (2018) were used by the authors to calculate a D4 TMF value in a marine estuary (Bohai Sea) in northeast China. The authors compiled field biota concentration data on a wide variety of organisms in the ecosystem, but only present TMF plots for a single food web chain (see Fig. 5 of Xue et al. 2018), more specifically: planktons (TL = 2.14) → ark shell (TL = 2.78) → Neverita's albumen (TL = 2.95) → Chinese ditch prawn (TL = 2.98). The paper failed to provide TMF values based on other food chains. Furthermore, the single food

chain that was examined for deriving TMF values was based on small sample sizes of biota (*e.g.*, n= 1 for ark shell and n= 2 for Chinese ditch prawn) and the spread of trophic levels was only 0.85, far less than the desired trophic level spread of >2 for TMF calculation (Kidd et al. 2019). Since the real food-web in the test area is complex by nature, it is highly unlikely the simple, single food chain would represent environmental reality, and the small sample sizes of some of the biota in the examined food chain are too small to account for expected environmental variability (Borgå et al. 2012). Additionally, as the authors acknowledge, the enrichment relationship between the two isotopes (^{13}C and ^{15}N) was not strong, and a proper food chain could not be established with any confidence. These data do not support that the samples taken for this study are reflective of an existing food chain; therefore, calculation of TMF values from these samples is not supported as environmentally relevant.

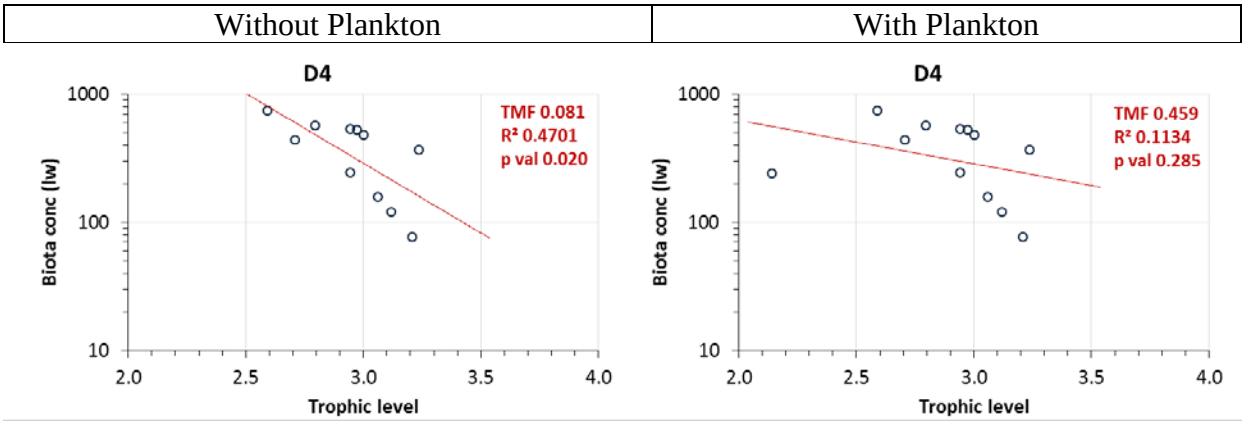
In addition, regarding the specimen masses in the food chain, the prey-predator relationship in the food chain is unusual. The only ark shell collected was an individual with a mass of 71 g (not clear if this was with or without shell), but the predatory snail, *Neverita albumen*, which the authors indicated is the major predator of the ark shell, had masses ranging from 2.1 to 4.7 g, with one individual of 17.9 g. The "apex predator" of this food chain is the Chinese ditch prawn with specimen masses ranging from 1.0 to 3.7 g. Although the ark shell → Neverita's albumen → Chinese ditch prawn may be a feasible food chain in this ecosystem, it seems highly unlikely that the individual specimens collected and analyzed here are reflective of that food chain. Individual size and life stage need to also be taken into consideration.

Thus, it is strongly recommended to use all the data for TMF calculation because the real food-web is intrinsically incorporated in the assessment. Kidd et al. (2018) also suggested key principles for evaluation of TMF studies including a minimum food web TL difference of 2.0 and balance in the number of samples for low and high trophic level species. Using all the data in Table 2 of Xue et al. (2018), Kim et al. (2019) recalculated TMF as shown in Table 3-9. Plots of D4 biota concentrations vs. trophic level shown in Figure 3-2.

Table 3-9. Recalculation of trophic magnification factors (TMFs) by Kim et al., (2019) using all the biota data of Shuangtaizi estuary, China, in Table 2 of Xue et al. (2018)

	Without plankton			With plankton			
cVMS	**TMF**	R^2	*p* value	**TMF**	R^2	*p* value	**TMF (Xue 2018)**
D4	**0.081**	0.4701	0.02	**0.459**	0.1134	0.3	Not provided

Figure 3-2. Biota concentrations of D4 (ng/g-lw) vs. trophic level (Kim et al., 2019), using all data (Xue et al. 2018)



Cui et al. (2019) examined the TMF behavior of cVMS materials in marine food webs the Chinese Bohai Sea; the food webs consisted of seabirds, fish, invertebrates, and zooplankton. The study area is highly urbanized and the authors acknowledge that the sampling locations are influenced by several major ports, which could contribute to spatial variability in environmental concentrations in cVMS and corresponding concentrations in biota. The authors were uncertain whether biota were exposed to the same cVMS concentrations at four different sampling sites, however. Migration of the seabirds, Saunder's gull and Herring gull, is well known, as most gull species are migratory, with birds moving to warmer habitats during the winter, though the extent to they migrate varies by species. This movement can also result in irregular and variable concentrations of cVMS in such species.

In addition, the enrichment relationship between the two stable isotopes (^{13}C and ^{15}N) used for trophic level determination was not strong, indicating that a proper food chain could not be established with any confidence (Cui et al. 2019). Specifically the C:N adjusted δ13C values of

Saunder's gull and Herring gull were -19.8 to -24.8 and -20% to -24.2%, respectively, which may indicate that the birds were feeding at different carbon/energy substrate foodwebs, leading to an overestimate of TMF for the foodwebs that include the seabirds. When seabirds are excluded from TMF analysis, the slope of the D4 biota concentration versus trophic level regression was not statistically significant (correlation coefficient or $R^2 = 0.04$), indicating no evidence of trophic magnification or dilution in the aquatic food webs for the Chinese Bohai Sea data of Cui et al. (2019).

A report from the Norwegian Environment Agency (Ruus et al., 2019) examines the cVMS concentrations in Inner Oslofjord biota. The authors concluded that the concentrations of siloxanes (D4, D5 and D6) displayed "*no significant relationship with trophic position*".

In summary, the available field data with regard to D4 and trophic magnification indicate the conclusion reached by Bridges and Solomon (2016) from their weight-of-evidence evaluation of biomagnification of D4 is still valid in studies published post 2016: this compound does not biomagnify in aquatic food webs and its field biota concentrations do not display any significant relationship with trophic position. Information on field study (and lab) bioaccumulation is provided in Table 3-10, with the corresponding reviews in Appendix B.

Table 3-10. Bioaccumulation based on laboratory and field studies

Method	Property	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from CSR)	Reference	Reference ID
Laboratory Studies							
OECD and EPA guidelines for laboratory feeding study with rainbow trout (*O. mykiss*) over 77 days	BMF†, lipid adjusted BMF, elimination half life	Elimination half-lives of approximately 20 d. BMF and BMF_L values of 0.28 and 0.66 for D4	Laboratory analysis with fish feed containing 500 µg/g of D4 in feed. Fish were fed once a day.	22 based on score of 17 to 68*	N/A	Woodburn et al. 2013	WOODB13A
Laboratory bioaccumulation study with fish (*Cyprinus carpio*) Field study of food web Shuangtaizi estuary in northeastern China	BCF, BMF, TMF	Published BCF for D4 with carp: 6,197 L/kg indicating strong bioaccumulation potential in common carp. The BMF value for D4 was 3.2.	Water and biological samples underwent extraction and underwent GC-MS. Fish concentrations reported as dry weight (dw) data, not wet weight (ww) data, as required for use in BCF modeling (i.e., OECD 305 Guideline). Reproduction of published fit of fish/water data to BCF model was not possible. Re-analysis of fish and water data resulted in revised BCF_k value of 1673 L/kg ww. Stable nitrogen (15N) and stable carbon (13C) isotope analyses were performed on muscle tissue samples to determine trophic levels. Lack of feeding of fish during 64 days of exposure could have affected the results.	32 based on score of 17 to 68*	N/A	Xue et al. 2018	XUE18A and XUE18B (SI)

Method	Property	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from CSR)	Reference	Reference ID
Field Studies							
Field study of biomagnification/biodilution	cVMS concentrations in pelagic food web measured by Purge and Trap extraction method followed by gas chromatography/mass spectrometry (GC/MS) calculation of TMFs for one Norwegian lake. Similar approach was taken for better known contaminants, PCB and BDE congeners.	D4 concentrations were too low to calculate TMFs; however, TMFs of 0.6 to 1.3 are provided in ECHA's dossier using reporting limits.	Representatives of the pelagic food web were collected in a large lake in Norway. Whole samples of zooplankton, and muscle samples of fish were analyzed for stable isotopes, cVMS, lipid content, and select PCB and BDE congeners for comparison to cVMS. However, there was a low sample number (n=4-5). The cVMS extraction method used in this study was found to be unreliable compared to other methods and most of the samples had D4 concentrations below the LOQ.	31 based on score of 15 to 60* Reviewed by Bridges and Solomon (BRIDG16A) and scored 2.95 for methods, 2.17 for relevance	2 in ECHA Dossier; not scored in CSR	Borgå et al. 2012	BORGA12A and BORGA12B (SI)
Field study of biomagnification/biodilution	cVMS concentrations in pelagic food web measured by a refined Purge and Trap extraction method followed by GC/MS to calculate TMFs in three Norwegian lakes. Similar approach was taken for better known contaminants, select chlorinated pesticides, PCB congeners and BDE congeners.	Low D4 TMF of 0.7 (0.5-0.9)	Representatives of the pelagic food web were collected in a three lakes (2 impacted, 1 remote) in Norway. Whole samples of zooplankton and muscle samples of fish were analyzed for stable isotopes, cVMS, lipid content, and select chlorinated pesticides, PCB congeners, and BDE congeners for comparison to cVMS. However, there was a low sample number (n=1-9). The cVMS extraction method was refined but has not been validated and most of the samples had D4 concentrations below the LOQ, except at one of the lakes.	31 based on score of 16 to 64* Reviewed by Bridges and Solomon (BRIDG16A) and scored 3.35 for methods, 2.17 for relevance	2 in ECHA Dossier; not scored in CSR	Borgå et al. 2013	BORGA13A and BORGA13B (SI)
Field study of biomagnification/biodilution; characterization of freshwater sediment and biological samples from a lake	Relative trophic levels, trophic magnification factor (BMF), predator/prey BMF, bioaccumulation factors (BSAF)	Trophic magnification factors (TMFs) for D4 were < 1	Lake Pepin, MN, USA. Lake Pepin is 102 km^2 in size, was used as a model freshwater lake system to collect biological and sediment samples.	21 based on score of 16 to 64* Reviewed by Bridges and Solomon (BRIDG16A) and scored 3.30 for methods, 3.00 for relevance	N/A	Dow Corning Corporation 2009c (Study Authors: Powell and Woodburn)	DOWCO09C

Method	Property	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from CSR)	Reference	Reference ID
Field study of biomagnification/biodilution; – characterization of lake sediment and fish tissue content	Concentrations of D4, D5, and D6 determined.	Analytical method detection limits expressed on the basis of wet weight across all matrices (sediment, zooplankton, and fish) ranged from 0.47 to 0.90 ng/g ww for D4.	cVMS concentrations were determined from field samples (Lake Opeongo, Ontario) and not prepared in the lab. Characterization of lake (sediment) was reported. Data included sediment characterization (carbon coulometry analysis, loss-on-ignition analysis), fish characterization (water and lipid content, stable isotope analysis), cVMS analysis (extraction from sediments, fish, zooplankton) Study had cVMS contamination in all reagent blanks.	36 based on score of 17 to 68* Reviewed by Bridges and Solomon (BRIDG16A) and scored 2.95 for methods, 2.00 for relevance. Method score downgraded to 1.48 due to variability in analytical data	N/A	Dow Corning Corporation 2010a (Study Author: Powell)	DOWCO10A
Field study of biomagnification/dilution; characterization of sediment and biological tissue content	Concentrations of D4, D5, and D6 determined.	TMF < 1.0 for D4	Evidence indicates that D4 does not biomagnify or bioaccumulate. Study site: Oslofjord, Norway	38 based on score of 17 to 68* Reviewed by Bridges and Solomon (BRIDG16A) and scored 3.05 for methods, 3.17 for relevance.	N/A	Dow Corning Corporation 2010b* (Study Author: Powell)	DOWCO10B*

Method	Property	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from CSR)	Reference	Reference ID
Field study of bioaccumulation/biodilution; characterization of marine sediment, seawater, effluent from municipal waste stream, and fish tissue content	Baseline concentrations of D4, D5, D6, and D7 determined.	mean concentrations of total methyl siloxanes were 46.1 ± 27.2 ng/L in seawater 12.4 ± 5.39 ng/g dry weight (dw) in sediment 5.10 ± 1.34 wet weight (ww) in fish mean value of biota-sediment accumulation factor (BSAF) was.0.716 ± 0.456 for D4	Study represented a one-time sampling event to determine siloxane concentrations in urban, semi-urban, and non-urban environments near Dalian China/Chinese Sea.	31 based on score of 16 to 64*	N/A	Hong et al. 2014*	HONG14A* and HONG15B (SI)
Field study of biomagnification/biodilution; collection of fish, crustaceans, mollusks, worms, and sea lettuce with laboratory analysis to determine concentrations and TMFs	TMF	Location: Dalian Bay, China TMF = 1.16 for D4.	Study collected multiple species from different levels in the food web to determine trophic magnification factors. The authors reported on a zooplankton-invertebrate-fish aquatic food web and trophic magnification was not statistically significant for D_4 (correlation coefficient or $R^2 = 0.02$, $p = 0.16$). These aquatic data indicate that neither trophic magnification nor trophic dilution was occurring with D4 in this aquatic food web.	30 based on score of 17 to 68*	N/A	Jia et al. 2015*	JIA15A* and JIA15B (SI)

Method	Property	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from CSR)	Reference	Reference ID
Field study of bioaccumulation	cVMS concentrations in benthic organisms and sediments for multi-media bioaccumulation factors (mmBAFs) measured by Purge and Trap extraction method followed by GC/MS. Also measured PCBs as a benchmark to evaluate cVMS data.	Sediment/benthic biota bioaccumulation ratio of D4 relative to those for PCB180. Study showed that D4 bioaccumulates to a greater extent (6 x in ragworm and 14x in flounder) than PCB180, but all of the sediment D4 concentrations and many of the biota D4 concentrations were below the LOQ.	Samples of flounder, ragworm and sediment were collected from six intertidal sites in the Humber Estuary (UK) and used to estimate bioaccumulation of cVMS and PCB congeners to worms and flounder in the estuary. However, the sample size was low, and D4 was below the LOQ for all of the sediment samples and many of the biota samples. Also bioaccumulation factors were not provided in a useful format; they were compared to PCB180 as a reference compound, but there is some doubt that D4 and PCB180 are distributed similarly in those sediments given that PCBs are legacy POP and cVMS are still being used and concentrations are likely to be distributed in a gradient from an anthropogenic source. Finally, the cVMS extraction method used in this study was found to be unreliable compared to other methods.	43 based on score of 15 to 60* Reviewed by Bridges and Solomon (BRIDG16A) and scored 2.55 for methods, 2.17 for relevance. Method score downgraded to 1.28 due variable recoveries	Not presented in ECHA Dossier or CSR	Kierkegaard et al. 2011	KIERK11A and KIERK11B (SI)
Field study of bioaccumulation and biomagnification/biodilution	cVMS concentrations in herring and blubber of grey seals from the Baltic Sea measured by Purge and Trap extraction method followed by GC/MS.	D4 was 4x lower in seal blubber than in fish samples, showing that D4 did not biomagnify.	Samples of herring and seal blubber were collected from Baltic Sea for cVMS determination. Herring muscle contained a mean concentration of 12 ng D4/g lipid weight. To assess biomagnification of cVMS, the lipid-normalized concentrations in herring were compared with the concentrations in seal blubber, but D4 concentrations in herring sampled in the same years as the seals were the below the LOQ. The median concentration of D4 in herring from the previous year was 4x higher than the median concentration in seal blubber suggesting that D4 did not biomagnify in grey seals. However, the sample size was low, and D4 was below the LOQ for the blubber samples. Finally, the cVMS extraction method used in this study was found to be unreliable compared to other methods	39 based on score of 15 to 60* Reviewed by Bridges and Solomon (BRIDG16A) and scored 2.80 for methods, 1.33 for relevance. Method score downgraded to 0.70 due to several factors	Not presented in ECHA Dossier or CSR	Kierkegaard et al. 2013	KIERK13A and KIERK13B (SI)

Method	Property	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from CSR)	Reference	Reference ID
Preliminary field study in Lake Storvannet in Hammerfest in northern Norway of bioaccumulation and biomagnification/biodilution and data collection for model development	cVMS concentrations in sediment, surface water, zooplankton, benthic fauna, sticklebacks (fish), brown trout, and char measured by gas chromatography/mass spectrometric detection (GC/MS).	Data were collected to develop a model to predict fate and bioaccumulation of cVMS in colder aquatic systems. Only predicted concentrations were reported, in graphical format.	Little detail on the study was provided in this paper; thus, Krogseth et al. (2017) should be considered instead.	47 based on score of 15 to 60*	Not presented in ECHA Dossier or CSR	Krogseth et al. 2014	KROGS14A
Field study of bioaccumulation and biomagnification/biodilution	cVMS concentrations in benthic fauna, sticklebacks (fish), brown trout, and char measured by GC/MS.	Average concentrations of D4 in whole *Pisidium*, *Chironomidae*, and sticklebacks were 4.7, 9.9, and 13 ng/g wet weight, respectively. Muscle concentrations of D4 in Arctic char ranged from below the LOQ to 19 ng/g wet weight; muscle concentrations of D4 in brown trout were all below the LOQ. These data suggest that D4 does not exhibit trophic biomagnification. D4 BSAF for char was <6.2. D4 was nondetect in trout, so no BSAF was calculated. D4 BSAF for sticklebacks was 1.5 (0.5-3.3).	Representatives of the food web were collected in a subarctic lake in northern Norway. Whole samples of benthic fauna (not depurated), whole samples of sticklebacks, and muscle samples of Arctic char and brown trout were analyzed for stable isotopes, cVMS, lipid content (fish only). However, there was a low sample number for the benthic infauna (n=2) and sticklebacks (n=5). In addition, the model under predicted cVMS concentrations in the benthic fauna, but did a better job predicting fish tissue concentrations.	33 based on score of 16 to 64*	Not presented in ECHA Dossier or CSR	Krogseth et al. 2017	KROGS17A and KROGS17B (SI)
Field study of biomagnification/dilution; characterization of biological samples from various food web compartments	TMF, biological concentrations	D4 concentrations in biota: Plankton = 2 ng/g (below limit of detection) Mayfly = 7 ng/g Fish 9-13 ng/g TMFs for D4: All species: 0.74 All species except plankton: 0.73 All species except plankton and walleye: 1.1	Samples collected in Lake Erie (Canada); thorough use of controls, spiked samples, and blanks.	31 based on score of 16 to 64* Reviewed by Bridges and Solomon (BRIDG16A) and scored 3.25 for methods, 3.17 for relevance	N/A	McGoldrick et al. 2014a*	MCGOL14A* and MCGOL14D (SI)

Method	Property	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from CSR)	Reference	Reference ID
Field study of cVMS occurrence in biota; characterization of fish tissue content	Concentrations of D4, D5, and D6 determined.	D4, D5, and D6 were detected at levels above detection limits in all 87 fish samples. D4, D5, and D6 were present at measureable but low levels in nearly all procedural solvent blanks and averaged 0.81 ng/g D4. The levels of D4, D5, and D6 in fish were highest in the Laurentian Great Lakes particularly in Lake Trout from Lake Ontario and the eastern basin of Lake Erie. Lake Ontario had the highest siloxane values, with D4 ranging 2.5 – 28 ng/g ww.	Field work in Canadian lakes assessing concentrations in lake trout and walleye.	31 based on score of 16 to 64*	N/A	McGoldrick et al. 2014b*	MCGOL14B* and MCGOLD14C (SI)
Field study of trophic dilution and magnification in Tokyo Bay, Japan using biological and sediment samples	Bioaccumulation, TMF, cVMS concentrations	There was no evidence from any of the regression models to suggest biomagnification of cVMS in Tokyo Bay.	The regression models indicated that trophic dilution of cVMS, not trophic magnification, occurred. Study in agreement with previous published literature.	25 based on a score of 16 to 64*	N/A	Powell et al. 2017	POWEL17A and POWEL17B (SI)
Field study of biomagnification/dilution; characterization of sediment and biological tissue content	Concentrations of D4, D5, and D6 determined.	TMF < 1.0 for D4	Peer reviewed version of DOWCO10B. Peer reviewed literature version not reviewed.	N/A	N/A	Powell et al. 2018	POWEL18A
Field study of trophic transfer in Bohai Sea, China. 17 species plus zooplankton were collected and analyzed for D4 .	Concentrations of D4, D5, D6, and D7, TMF, and trophic dilution.	TMF based on regression of lipid-normalized concentrations and TL for all species was 1.7 for D4. The TMF based on the zooplankton-invertebrate-fish (excluding seabirds) was not significant for D4.	Field work in marine environment assessing concentrations in various species to understand trophic transfer.	28 based on score of 16 to 64*	NA	Cui et al. 2019	CUI19A

Method	Property	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from CSR)	Reference	Reference ID
Field study in inner Oslofjord, Norway, on marine food web and multiple contaminants, including siloxanes	Concentrations of D4, D5, and D6, and numerous other compounds such as PCBs, metals, etc.	D4 tissue concentrations were not detected in lower trophic level organisms (e.g., polychaetes, blue mussel, krill, prawn and herring), or in herring gull blood or eggs, but concentrations in cod ranged from 16.2 to 130 ng/g ww. Concentrations of siloxanes (D4, D5 and D6) displayed no significant relationship with trophic position	Field work in marine environment assessing concentrations in various species to understand urban impacts to marine ecosystem.	29 based on score of 16 to 64*	NA	Ruus et al. 2019	RUUS19A
Field study of trophic transfer in Lake Champlain, USA.	Concentrations of D4, D5, and D6 in biota and sediment. Sediment samples were also characterized for physical chemical properties.	Concentrations of cVMS in biota were highly variable within and between species, and generally appeared to be related to sample collection location.	Field work in freshwater environment assessing concentrations in various species to understand TMF across seven trophic guilds.	23	NA	Powell et al. 2014	DOW14A

*Modifications to the scoring system are noted when categories were not applicable and no score was made. See more scoring details in Appendix B.
†Abbreviations: BAF–bioaccumulation factor; BCF–bioconcentration factor; BMF–biomagnification factor; BSAF–biota sediment accumulation factor; TMF–trophic biomagnification factor
[1] These studies include a range of possible scores between 18 and 72. A higher score indicates a lower reliability. Blue indicates high reliability, yellow indicates medium reliability, pink indicates low reliability, and no color indicates scoring not applicable.
[2] Peer-reviewed articles with a supplemental information (SI) that was reviewed are noted. The SI is documented as a separate document (e.g., KIM16A is main document and KIM16B is the SI). SI's are not listed in the references.

4 Scope of the Evaluation

This section discusses the scope of the D4 Risk Evaluation. The conditions of use that are included, as well as those that are excluded, are presented. This is followed by a discussion of the conceptual models that describe the potential exposure pathways for D4 that could result in hazards to human health and the environment. Finally, an analysis plan is presented which discusses the sources of data to inform the potential exposures and how these data will be used.

4.1 Conditions of Use

TSCA § 3(4) defines conditions of use as "the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of." Sources of information on conditions of use for D4 include the CSR (2018), the *D4 and D5 Conceptual Site Models and Mass Balance Report* prepared by ERM for the Silicones Environmental, Health and Safety Council (SEHSC; ERM 2012) and the results of the US EPA 2016 Chemical Data Report (CDR).

The life cycle diagram for D4 is presented in Figure 4-1. Manufactured D4 is principally used as a chemical intermediate in the production of polymers. Manufactured D4 is also incorporated into a formulation, mixture, or reaction product, which is then used in a wide range of industrial and consumer applications, such as personal care products, household products, electronics and textiles applications. Uses in food contact materials, cosmetics and personal care products, and over the counter medication (OTC) do not fall under TSCA but are governed by other regulations and are technically not included in a TSCA risk evaluation. However, these uses are considered in Section 5.1 of the Exposure Assessment as a conservative approach. The categories of the conditions of use that are included in the risk evaluation are presented in Table 4-1.

Figure 4-1. D4 Life Cycle Diagram

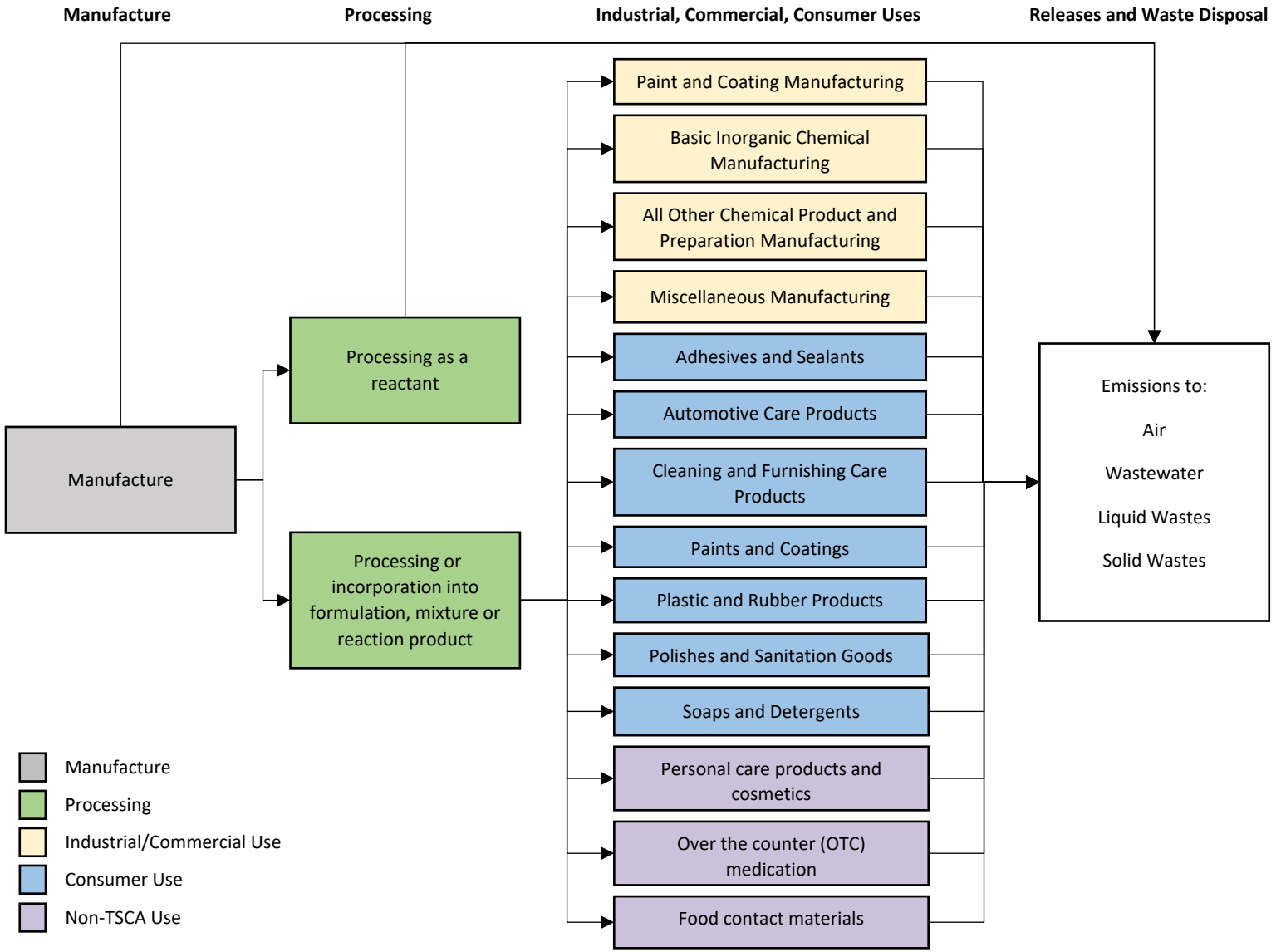


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Table 4-1. Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation

Life Cycle Stage	Category [a]	Subcategory [b]
Manufacture	Domestic Manufacture	Domestic Manufacture
Processing	Processing as a reactant	All Other Basic Organic Chemical Manufacturing
		Other Basic Organic Chemical Manufacturing
		All Other Basic Inorganic Chemical Manufacturing
		All Other Chemical Product and Preparation Manufacturing
		Resin and Synthetic Rubber Manufacturing
		Synthetic Rubber Manufacturing
		Adhesive manufacturing
	Processing-incorporation into formulation, mixture, or reaction product	Paint and Coating Manufacturing
		All Other Basic Inorganic Chemical Manufacturing
		All Other Chemical Product and Preparation Manufacturing
		Miscellaneous Manufacturing
Commercial/Consumer Use	Adhesives and sealants	
	Automotive care products	
	Cleaning and furnishing care products	
	Paints and Coatings	
	Personal care products and cosmetics[c]	
	Over the counter (OTC) medication[c]	
	Food contact materials[c]	
	Plastic and Rubber Products not covered elsewhere	
	Polishes and sanitation goods	
	Rubber and plastic products	
	Soaps and detergents	
Disposal		

[a] These categories of conditions of use reflect CDR codes and broadly represent conditions of use of D4 in industrial and/or consumer settings.

[b] These subcategories reflect more specific uses of D4.

[c] These categories are not TSCA-relevant, but per Section 5.1 are considered in the Exposure Assessment as a conservative approach.

4.1.1 Domestic Manufacture

The starting point for silicone (siloxane) manufacture (including D4) is quartz rock, a pure form of silica (SiO_2). Silica is mixed with coke and reduced to silicon metal by heating to temperatures of 2,200 °C in an electric arc furnace. The chemical reaction is:

$$SiO_2 + 2C \rightarrow Si + 2\ CO$$

Commercial production of silicones is currently done by the "Direct" process (also known as the "Rochow Process" or Mueller-Rochow Process"), in which ground silicon metal reacts with methyl chloride (CH_3Cl) vapor (in the presence of proprietary copper catalysts) in a fluid-bed reactor to form a mixture of methylchlorosilanes (and other by-products), principally dimethyldichlorosilane, trimethylchlorosilane, and methyldichlorosilane, which are all intermediates used to make other final products. For example, the chemical reaction producing dimethyldichlorosilane is:

$$Si + 2\ CH_3Cl \rightarrow (CH_3)_2SiCl_2$$

These chlorosilanes are separated by fractional distillation.

Chlorosilanes are hydrolyzed, a reaction that produces silanol intermediates and hydrogen chloride (HCl). The hydrolysis reaction is described generically by the reaction:

$$R_xSiCl_{(4-X)} + 4\text{-}x\ HOH \rightarrow R_xSi(OH)_{(4-X)} + 4\text{-}x\ HCl$$

Where R= methyl, phenyl, vinyl, etc.

The HCl is captured and separately reacted with methanol (CH_3OH) to form methyl chloride, which is one of the starting chemicals in the direct process described above. The silanol intermediates undergo condensation *in situ* to produce mixtures of linear and cyclic siloxanes, commonly known as condensate. In particular, silanols are capable of condensation reactions of the type to produce a siloxane (a compound with the structure Si-O-Si) and water:

$$R_3SiOH + HOSiR_3 \rightarrow R_3Si\text{-}O\text{-}SiR_3 + HOH$$

Depending upon the structure of the silanols, either simple condensation or condensation polymerization can take place. The silanol condensate is further processed, split, or distilled into linear or cyclic siloxanes, such as D4.

The overall reactions, including the reduction of quartz to silicon, reaction of silicon metal with methyl chloride to produce chlorosilanes, the hydrolysis of chlorosilanes, and the condensation of siloxanes to produce oligomers and polymers summarize the process route for producing siloxane compounds.

4.1.2 Processing

4.1.2.1 Processing as a Reactant

The principal use of D4 is as a monomer in the formation of silicone polymers, most especially polydimethylsiloxane (PDMS). A key process in the manufacture of silicone polymers is the conversion of short-chain linear or ring siloxanes (oligomers or polymers) under equilibrium conditions via the continual breaking and reforming of Si-O-Si bonds using either strong acid or base catalysis at temperatures up to *approx.* 430K. This is commonly called “equilibration polymerisation” as in most instances the equilibrium favors higher molecular weight silicone polymers with just 15% w/w cyclic remaining regardless of the make-up of the starting dimethylsiloxane mixture. It may be done under batch or continuous conditions (Wacker 2005).

Isolated, pure (typically 99%) D4 is a common raw material which is used for equilibration polymerisation to make not only PDMS but also, in combination with other siloxane co-monomers, a wide range of functionalised siloxanes bearing, for example, amine, SiH, or vinyl functional groups (Wacker 2005). Alternatively, blends of D4 and decamethylcyclopentasiloxane may be used (Bluestar 1997).

In addition to its use as a monomer, D4 can also be described as an intermediate. Thus, disiloxanes will also participate in the chain cleavage and re-formation reactions described above and so hexamethyldisiloxane, for example, will be cleaved and incorporated into the

growing polymer chain as an end-blocker. The ratio of hexamethyldisiloxane to -$(CH_3)_2SiO$- in the reactant feedstock effectively governs the molecular weight of the PDMS produced (Wacker 2005). Thus, if the relative ratio of hexamethyldisiloxane to -$(CH_3)_2SiO$- is very high, short oligomeric siloxanes which do not meet the criteria required to be classed as a polymer may be prepared via the processes described above.

An example of this is the production of decamethyltetrasiloxane, which may be prepared by the equilibration of hexamethyldisiloxane and D4. The equilibration is catalysed by a solid acid such as an acid clay or resin. The siloxanes are fed to the reactor in a continuous fashion and allowed to reach equilibrium. This equilibrate is removed from the reactor, and so from contact with the catalyst which prevents further bond cleavage and is then distilled twice. In the first stage, more volatile siloxanes (e.g., unreacted hexamethyldisiloxane and D4) are removed as the overhead fraction and returned to the reactor. In the second stage, the desired product is collected as the overhead fraction, which may be filtered and sent to storage or for packaging. Less volatile siloxanes may be returned to the reactor.

4.1.2.2 Processing - Incorporation into Formulation, Mixture, or Reaction Product

Use in non-metal surface treatment

The surface of minerals or other non-metals is often treated in order to change the surface chemistry or energy without affecting the properties of the bulk basis substance: thus, a hydrophilic surface may be rendered hydrophobic or an inert surface made reactive. Although organofunctional silanes, including chlorosilanes and silazanes, are the most common class of Si-based substances used to treat non-metal surfaces, siloxanes are also used, most especially in the treatment of silica to render it hydrophobic when used in a silicone polymer matrix (e.g., silicone elastomer). If a cyclic siloxane with no ready functional group to attach it to the silanols of the substrate surface, such as D4, is to be used, sufficient energy or chemical activation has to be provided. Thus, two possible processes are possible:

- the surface may be “pre-treated” as one step in the manufacture of the modified substance, such as a filler, before it is sold or further processed, or

- the treating agent may be added *in situ,* either concurrently or consecutively to the basis substance and other components of the system.

Pre-treatment during manufacture

The principal pyrogenic (or fumed) silica manufacturers supply untreated, hydrophilic silica but also several grades of treated, hydrophobic silica. D4 is used as a surface treatment agent for this purpose. The surface reaction is described as being done with the treating agent (Si-based substance) “in the gas phase” and in a direct, continuous fashion, i.e., the surface treatment process is directly integrated with the silica production process.

In-situ treatment

In-situ treatment is commonly used in the production of silicone rubber compounds where a mixture of high molecular weight (MW) silicone polymer, pyrogenic silica, and surface treatment agent are mixed under high shear to form a “rubber base”. This most usually occurs in a batch process. Production unit sizes vary but a volume of 1,000 – 5,000 liters is not atypical. Addition levels are of the order 0.2 to 1.0% by weight of the treating agent of the total mix.

Use in electronics applications

Three distinct applications have been identified for use of D4 in the electronics and semiconductor manufacturing industries:

- Precursor for chemical vapor deposition
- Ingredient of conformal coatings
- Ingredient of potting agents (or encapsulants)

Precursor for chemical vapor deposition

Forming electronic devices on a wafer involves a long series of highly precise processes. Many of these operations consist of depositing and then patterning layers, and various Si-based substances are used in these processes, for example, one class of interlayer dielectric is based on a solution of hydrogen silsesquioxane resin, $(HSiO_{3/2})_n$, in a carrier solvent, which may itself be a blend of volatile methylsiloxanes (VMS). These coatings are applied by spin coating.

An alternative process is chemical vapor deposition (CVD) whereby one or more gas or liquid precursor materials are carried by an inert gas stream into a deposition chamber containing the wafers. The precursors react and attach themselves to the wafer surface, gradually building a layer of the desired composition until the desired thickness of the new thin film has been achieved. This is an industrial batch process, but everything is totally contained, and clean-room facilities are maintained throughout in order to protect the semiconductor product from contamination. This also effectively protects the workers from molecular and particulate contaminants.

The CVD process takes place in a process chamber or a quartz tube under low pressure at temperatures of >1000°C. The process reaction takes place in a small process chamber or tube under vacuum conditions and is fully automated. Each batch process uses only a small volume of precursor (70–150 ml). The precursor reacts on use**.** The chamber and tubes are automatically purged with inert gas (nitrogen or helium) to remove any unreacted precursor before opening the chambers to remove the wafers. They are then cleaned after each process cycle with cloths wetted with water and alcohol to remove deposits of amorphous silicon dioxide. Thorough manual cleaning of process chambers is performed on a biweekly or monthly basis, but no unreacted precursor is present in the chamber at this point. All chambers are vented to the wet scrubber.

Conformal coatings and potting agents

Potting agents (or encapsulants) are gels or elastomers which fill recessed cavities of an electronic substrate and extend over the outer edge to completely seal the substrate in its housing and encapsulate the terminals. These are often supplied as two-part systems which are mixed *in situ*.

Conformal coatings such as polyurethanes, acrylics, epoxies, and silicones have been used for over 40 years to protect electronic circuits. The two key functions of coatings used in electronic circuits are environmental protection, particularly moisture protection, and electrical insulation or isolation. In addition to shielding electronics from moisture, chemicals, and contaminants that result in corrosion and electrical failures, environmental protection includes protection from

physical abuse, such as handling and abrasion, temperature extremes, and radiation. However, the one coating requirement that is basic to all functions is good adhesion, both initially and during the operation and lifetime of the hardware.

Conformal coatings can be formulated using many different chemistries and are normally applied by spraying, dipping, brushing, or flow coating. Early formulations that were based on solvent carriers and long cure times are being replaced with non-solvent containing (100% solids) compositions and formulations that cure in minutes instead of hours. Using non-solvent formulations is important in avoiding the entrapment of solvents in the coating which can cause voids and loss of adhesion. Traditional highly volatile organic solvents are being replaced by solvents having low VOC (volatile organic compounds) emissions.

Silicone coatings may be either solvent-based or solventless (100% solids) and either one-part or two-part systems. For electronic applications, the one-part, solventless (100% solids) formulations are preferred. One-part silicones generally cure by exposure to ambient moisture. As mentioned above, silicone coatings are primarily polymeric. The silicone polymers used in electronics applications are often referred to as being of “high purity” and/or described as “non-migrating.” This is indicative of their containing a very low level of incidental, volatile cyclic siloxanes (Licari 2003).

Use in textiles applications

Within the textile and leather finishing industries, silicone polymers likely to contain D4 are used in several applications, including:

- Functional finishing agents
  - Fabric softeners
- Coating, wholly or partially, of textiles or finished articles with silicone rubber, including outdoor clothing, air bags and conveyor belts.
  - Solvent born coatings for leather
  - Anti-shrink and waterproofing coatings

  - LSR (Liquid Silicone Rubber) and RTV (Room Temperature Vulcanised) coatings for stocking tops, bras, socks *etc.*; for airbags for cars; or for architectural fabrics
  - LSR printing ink for textiles
- Processing aids such as defoaming/anti-foaming agents, lubricants, wetting agents or leveling agents.
  - Synthetic and cotton fibre spinneret lubricants

These applications are further discussed below.

Functional finishing agents

Silicone finishing agents are used to impart properties such as softening, water repellency, shrink-resistance, and abrasion resistance to textiles and leather.

Silicone polymers, including resins, have been used as water-repellent agents in the textiles industry since at least the 1960s. As well as imparting hydrophobicity, silicones have the added advantages of chemical resistance and softening or smoothing effects on the textiles (Noll 1968). The Reference Document on Best Available Techniques (BREF) on the textiles industry (EC 2002) describes the use of silicone repellents and silicone softeners during textile finishing treatments. Both types of product are usually supplied as aqueous emulsions of polysiloxanes – either PDMS or organo-modified polysiloxanes with reactive or non-reactive functional groups (EC 2002). Use of aminofunctional groups is now common due to increased physical adsorption on the textile substrate and greatly enhanced softening properties versus PDMS. These aqueous formulations generally also contain catalysts and organofunctional silane cross-linking agents.

Polysiloxane (polymers) contain cyclic siloxane residues, such as D4. Although these residues may undergo polymerisation or degradation (oxidation) in later processing, some will be released to wastewater and air.

A report produced by the Italian textiles industry (Federchimica, 2010) describes in detail the use of chemicals in the textile sector, including typical amounts used, common processes, and

handling techniques. The use of silicone softeners is identified at various life cycle stages, summarised in Table 4-2 below.

Table 4-2. Use of silicone softeners in textile applications

Textile processing step	Textile type	Range (g/kg)	Typical (g/kg)	Frequency of use[1]
Pre-treatment	Anti-shrink	0.5 – 1	Not stated	3
Dyeing	Protein fibres (wool)	0.2 – 3	1	4
	Cellulose fibres (cotton)	0.5 – 3	1	2
	Synthetic fibres	0.5 – 3	1	3
Finishing	Specialist treatment	0.5 – 6	1.5	4

1 = Always (100%); 2 = Often (75%); 3 = Medium (50%); 4 = Infrequent (25%)

Functional finishing auxiliaries are usually applied to textiles from aqueous solutions or dispersions, mainly in padding machines (continuous process), but also batch (exhaust) application, for example a winch beck.

Various types of padding machine are used, but the principle is that the fabric is drawn through a trough where it picks up the liquor, and then passes through a system of rollers. The amount of liquor picked up is dependent on the pressure applied by the rollers, and the liquid in the trough circulates to prevent differences in temperature or concentration. The liquid level in the trough automatically compensates for the liquor picked up by the fabric (EC 2002). The required amount of auxiliary added to the padding liquor for functional finishing ranges from 5 to 50 kg/ton, and is typically 20 kg/ton (OECD 2004).

The recommended concentration of finishing agent in the padding liquor is typically around 30 g/L. Thus, the concentrations for emulsions based on siloxanes (typically 10–40% actives) in the bath go from 10–100 g/l. This would translate to 1–40 g/l of siloxane actives in the bath. The level of siloxane actives deposited on the fabric is 0.1–1% based on the weight of the fabric.

Silicone water repellent treatments are also widely used in leather finishing. The leather may be immersed in solutions of impregnating agents in organic solvent for 0.5 to 2 minutes, or applied with brushes, rollers, or plush. For larger pieces of leather, the finishing chemicals may be applied by spraying (Noll 1968). Following impregnation, the leather is dried and then heated (50–60°C).

Coatings

Coated textiles are described as being a fabric substrate coated with a thin, flexible layer of natural or synthetic polymer which is applied as a dispersion or solution of polymer in organic solvent (OECD 2004). However, silicone elastomers are most often applied "neat" (100% actives). Techniques used include blade, spraying, or printing. The application amount varies depending on the required coating thickness, but in most cases is around 100 g/kg (OECD 2004).

The relevant polymer systems for this scenario may be described as:

- heat-vulcanizing silicone rubbers (HVR);
- LSR; or
- RTV.

End applications for the coated textiles range from industrial (conveyor belts, automotive airbags) to consumer ("hold up" stockings). While the polymers themselves are not being assessed, the presence of low levels of cyclic siloxanes, such as D4, as impurities must be taken into consideration.

Processing aids

Defoaming agents (or antifoaming agents) are needed at several stages of textile processing, during pre-treatment (*e.g.*, sizing, desizing, bleaching) and finishing operations (*e.g.*, application of fabric softeners, dyeing) (Table 4-3). Yarn needs to be sized before weaving to protect it from damage or breaking during the weaving process. Typical sizing agents include modified starches and cellulose, polyvinyl alcohol (PVA), polyacrylates or polyesters. Defoaming agents are added when the sizing agents tend to produce foams (e.g. PVA), or if wetting agents (usually surfactants) are used. The recommended concentration of defoaming agent ranges from 0.1 to 2% of a typically 10 – 30% aqueous dispersion or emulsion; some products require further pre-dilution in water before use (Company material safety data sheet [MSDS]). Typically, 1.5 g of silicone antifoam is required per kilogram of fabric (Federchimica 2010). The sizing agents must be removed from the woven fabric before finishing and this process is the main source of

discharge to waste water from finishing mills (OECD 2004). Defoaming agents are also needed during the removal of water-soluble sizing agents and to prevent unwanted foaming during dyeing or other finishing processes (EC 2002). These may be pre-added to surfactant formulations or added directly at the point of use.

Finally, dyes or especially softeners may be applied from aqueous emulsions which contain surfactants. Application conditions usually result in a certain degree of shear or agitation. Taken together, these conditions can give rise to unwanted foaming which may be controlled by addition of defoaming agents. Again, the recommended concentration of defoaming agent ranges from 0.1 to 2% of a typically 10 – 30% aqueous dispersion or emulsion; some products require further pre-dilution in water before use (Company MSDS). The typical loading rate is 1 g/kg fabric (Federchimica 2010).

The Federchimica report (2010) summarises typical product formulations and processes for each life cycle stage.

Table 4-3. Use of defoaming agents in textile applications

Textile processing step	Textile type	Range (g/kg)	Typical (g/kg)	Frequency of use
Pre-treatment	Anti-shrink	0.1 – 0.3	Not stated	3
	Sizing	0.05 – 0.2	0.1	4
	Desizing	1 – 10	1.5	1
	Synthetic fibres	0.5 – 30	10	2
Dyeing	Protein fibres (wool)	0.1 – 1.5	0.7	2
	Cellulose fibres (cotton)	0.2 – 2	1	3
	Synthetic fibres	0.2 – 1	0.5	3
Finishing	Specialist treatments e.g. water repellent	0.01 – 0.5	0.5	3
	Coating	Not stated	0.01	3

1 = Always (100%); 2 = Often (75%); 3 = Medium (50%); 4 = Infrequent (25%)

As with other applications described above, the defoaming agents themselves contain polymers in conjunction with other additives such as silica. The polymers are often polydimethylsiloxanes, which may contain low levels of cyclic siloxanes such as D4.

Another use of silicones as processing aids in the textile industry is to provide lubrication, for example to prevent adhesion of thermoplastic synthetic fibers to the spinneret during fiber production, or as needle lubricants to prevent overheating during sewing and again the polymers used are often polydimethylsiloxanes, which may contain low levels of cyclic siloxanes such as D4.

4.1.3 Commercial/Consumer Use

Si-based substances have numerous and diverse applications within household care products (e.g. washing and cleaning products, solid and spray-type polishes, wax blends, automotive aesthetics, paints and coatings, etc.). In addition, cleaning and polishing products used in a commercial, industrial or professional setting may also contain Si-based substances. The majority of Si-based substances used in these applications are silicone polymers or silicone resins. D4 is commonly present at >0.1% w/w in dimethylsiloxane polymers and copolymers and in the range 1-3% where these are made by emulsion polymerisation. Similarly, D4 may be present at >0.1% (but <1%) in decamethylcyclopentasiloxane which finds a variety of uses in household care products such as a solvent or carrier for other higher molecular weight silicone polymers or even as an environmentally friendly dry-cleaning solvent (Brooke et al. 2009; SEHSC 2008a).

D4 as such may also be used in some products, containing between 0.1 to >50% by weight, although the majority are in the range 1-5%.Again, these products are mostly preparations made by blending a set of ingredients in a particular order with particular levels of shear and temperature (the conditions are themselves often a trade secret), most usually in a batch process which could vary in unit capacity from a few hundred kilograms to several tons.

4.1.4 Uses Not Relevant for Risk Evaluation

The following conditions of use are not relevant for the risk evaluation for the reasons stated, and are further described below:

- Personal care products, food contact materials, and OTC medication – these uses do not fall under the scope of TSCA, which excludes any food, food additive, drug, cosmetic or device. Other regulations in the U.S. govern the use of chemicals in personal care products, in food contact materials (such as nipples for baby bottles containing infant formula), or in OTC medication. The Federal Food, Drug, and Cosmetic Act (FFDCA) regulates foods, drugs, medical devices, and cosmetics.
- Laboratory use – low volume use for which exposures to humans and the environment are managed through the use of personal protective equipment, institutional controls, and hazardous waste disposal requirements.

4.1.4.1 Personal Care Products, Food Contact Materials, and OTC Medication

In the category of personal care products, many of these products are silicone polymers (or emulsion polymers) which can contain low levels of D4 as an impurity: >0.1% w/w is probable and as much as 1-2% is not atypical, especially for emulsion polymers. Certain foods may contain D4 remaining after indirect food additives use such as the use of silicone-based antifoams in food processing. In addition, several OTC medications (vapor rub, anti-gas) may contain D4. These uses are regulated by the U.S. Food and Drug Administration (FDA) and do not fall under the purview of TSCA. However, scenarios for the human health exposure assessment have conservatively included them, as further explained in Section 5.1.

4.1.4.2 Use as a Laboratory Chemical

D4 is used as a reagent in both industrial and academic laboratories. In most instances, it is used as an intermediate in the synthesis of other Si-based chemicals or as a solvent / dispersant and so will fall broadly under the uses described above.

In any event, these uses are generally of low volume. Personnel handling D4 should be professionals (or students supervised by such professionals) with appropriate laboratory chemical hygiene and management training and familiarity with the handling of hazardous reagents, and with access to relevant risk management measures, such as fume hoods, which are sufficient to ensure adequate protection for workers in respect of any properties which are hazardous to humans or the environment. In addition, although the nature of individual uses will vary, it can be assumed that any waste or unused D4 is treated as hazardous waste and disposed of accordingly.

Laboratory use of D4 is not included in the D4 risk evaluation.

4.1.5 Emissions and Disposal

During manufacturing of D4, volatile organosilanes and hydrochloric acid are emitted as gases to some extent during the reactions, separations, storage, and loading operations. Those gases are collected by local exhaust ventilation systems and transported to abatement systems, including incineration and scrubbers, from which air emissions are vented to the atmosphere. Fugitive emissions may be produced throughout the facility, including in valves, pumps, drains, and the on-site wastewater treatment plant (WWTP), if present. The water produced in the reaction vessels and in the scrubbers is typically discharged to a wastewater storage tank, from which it may go to either an on-site treatment or a municipal WWTP. In either case, the treated water is discharged to a surface water body.

The sludge produced in an on-site WWTP and solid waste produced during the reaction and separation steps are disposed of at on-site landfills or shipped to off-site management systems. Depending on the type of solid waste, these management systems may include incinerators,

energy recovery systems or other beneficial use, or landfills. None of the biological sludge or other solid wastes is disposed of as fertilizer or via land application.

During formulating, local exhaust ventilation systems collect any gases produced and transport them to pollution control equipment (scrubbers, condensers, energy recovery systems), with a minimal portion of the incoming gases being released to the air as point sources. Fugitive air emissions may be produced throughout the facilities, in equipment such as storage tanks or containers, valves, and pumps. Wastewater is generally only produced during mixing and is either treated at an on-site facility (at D4 manufacturing or processing wastewater treatment systems) or discharged via sewer to a municipal WWTP. Solid waste is produced in both the mixing and packaging steps; this waste is sent off site for disposal, which may include thermal processes or landfilling.

All steps in processing (storage, reaction, and purification) are generally carried out in closed systems with local exhaust ventilation that collects and transports gases produced during the different processing steps to a recovery system to maximize the use of D4 raw materials. The waste gases produced in the recovery equipment are typically routed to abatement systems, including scrubbers, condensers, and energy recovery systems. Fugitive air emissions can be produced from on-site equipment such as valves, pumps, drains, or from an on-site wastewater treatment system, if present.

All processing steps may also produce wastewater, which is typically routed to a storage area from where it is discharged into an on-site WWTP, an off-site municipal WWTP, or pretreated in an on-site WWTP and then discharged to an off-site municipal WWTP. The solid waste produced during the reaction, recovery, and air emission abatement systems is shipped to an off-site waste management facility.

Table 4-4 summarizes the types of emissions for each type of facility.

Table 4-4. Types of emissions for each type of facility

Type of Facility	*Type of Emission*		
	To Air	*To Water*	*To Land*
Manufacturers	Air Emissions through Vents and Abatement Systems (Point Source Emissions)	On-site or Off-site WWTP Effluent	Solid Waste to Fuel Recovery
	Fugitive Air Emissions	Storm Water Discharge to Surface Waters	
Formulators	Air Emissions from Pollution Control Equipment (Point Source Emissions)	Wastewater to municipal WWTP or for Off- site Treatment	Waste from Operations
	Fugitive Air Emissions		Activated Carbon Waste for Fuel Recovery
Processors with no On-site WWTP	Point Source Air Emissions	Industrial Waste Water Discharge to municipal WWTP	Solid Waste Disposal to Off-site Waste Management
	Fugitive Air Emissions	Storm Water Discharge to Surface Waters	
Processors with On-site WWTP	Point Source Air Emissions	Treated Industrial Waste Water Discharge to Surface Waters	Solid Waste Disposal to Off-site Waste Management
	Fugitive Air Emissions	Storm Water Discharge to Surface Waters	
Processors with On- and Off-site WWTP	Point Source Air Emissions	Treated Industrial Waste Water Discharge to Off-site municipal WWTP	Solid Waste Disposal to Off-site Waste Management
	Fugitive Air Emissions	Storm Water Discharge to Surface Waters	

4.2 Conceptual Models

In this section, conceptual model diagrams are presented to reflect sources, release mechanisms, migration pathways, exposure routes, and potential receptors for D4 exposure in the workplace and through environmental releases. The diagrams summarize the following:

- Multimedia release pathways (primary and secondary, as applicable);
- Potential exposure routes specific to each medium (air, soil, surface water, sediment, groundwater, food items, occupational / consumer materials); and
- Receptors specific to each medium, including both human and ecological receptors where relevant.

Based on fate and transport properties of D4, only those pathways identified as complete, i.e., those pathways that lead to a reasonable expectation of potential exposure to human or ecological receptors, are shown on the diagrams.

4.2.1 Human Receptors

Several groups of human receptors are potentially exposed to D4: workers, consumers, and the general population. Worker exposure is addressed separately from exposures to consumers and the general population.

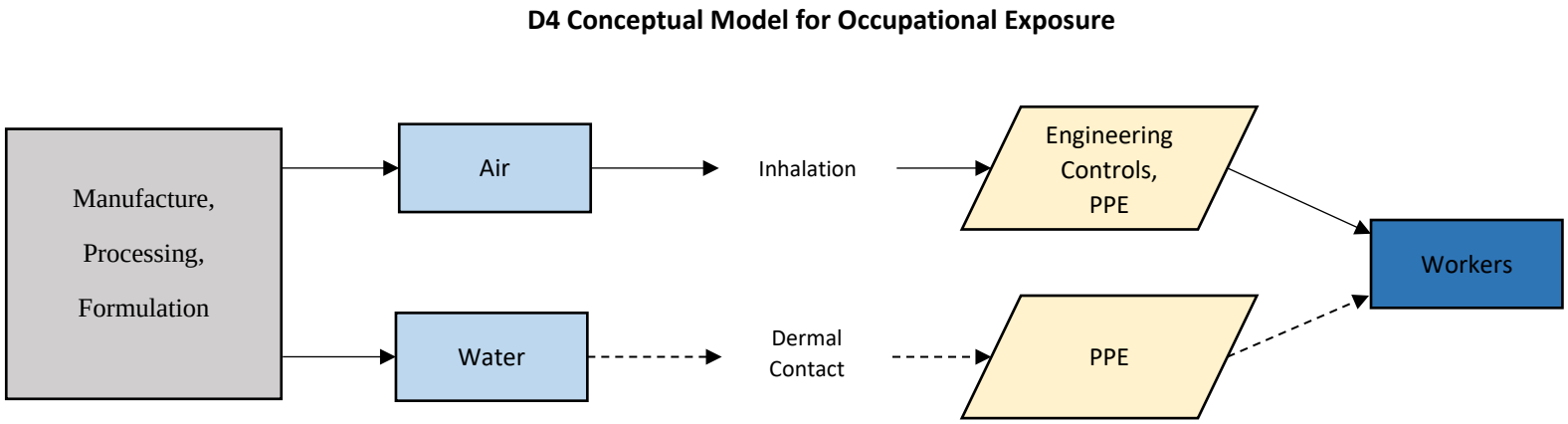
4.2.1.1 Workers

The Conceptual Model for workers engaged in manufacturing, formulation or processing is shown in Figure 4-2. The manufacture of D4 is in a closed system. Dermal exposure is mitigated through the required use of impervious gloves, uniforms, and safety glasses. Inhalation exposure is minimal due to the closed system and the use of general ventilation. Any potential exposures above the 8-hour time weighted average (TWA) of 10 ppm (Occupational Alliance for Risk Science (OARS) 2017) are mitigated by the use of air purifying respirators.

Worker monitoring (personal sampling) data are available for workers involved in the manufacture and processing of D4. Monitors were worn by workers during work shifts and concentrations were captured for potential air exposures.

In summary, the primary exposure pathway for workers engaged in D4-related manufacturing, processing, or formulation is inhalation. In addition, inhalation exposures by office workers, and inhalation / dermal exposures by barbers and beauticians during the application of personal care products are considered. As further discussed in Section 5.1.1, while exposures to office workers and barbers / beauticians are not relevant under TSCA, these exposures are included to provide a conservative occupational assessment.

Figure 4-2. D4 Occupational Risk Conceptual Model for Workers Engaged in Manufacturing, Formulation, and Processing



PPE personal protective equipment

Note: dashed lines indicate minor pathway under initial consideration

4.2.1.2 Consumers and General Population

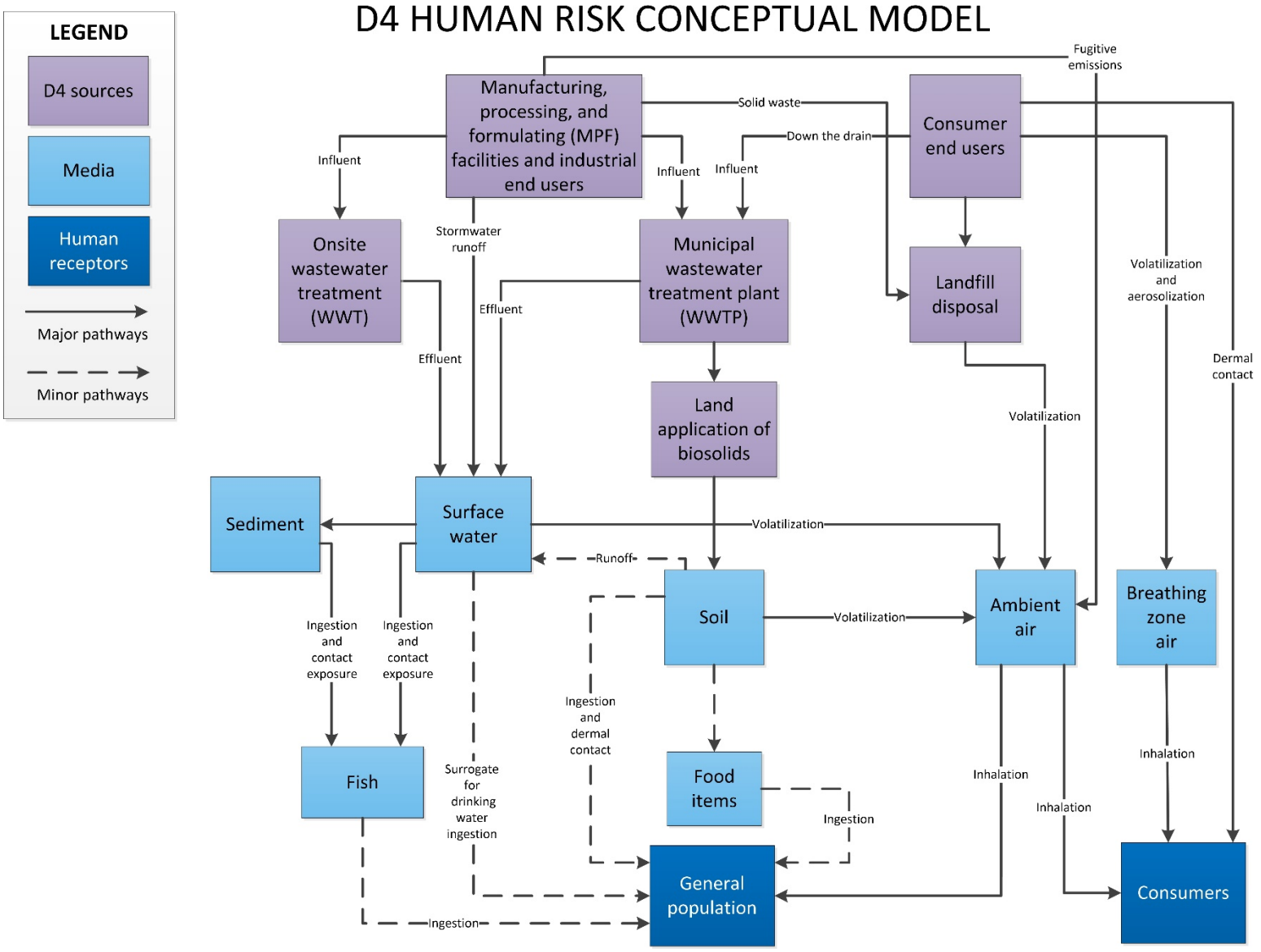
Figure 4-3 presents the Conceptual Model for human receptors other than workers, i.e., consumers and the general population. Manufacturing, processing and formulating (MPF) of D4 has the potential to release D4 into the environment and the general population may be potentially exposed through air, surface water, sediment and soil, either directly or indirectly.

In addition, D4 processed into polymer or formulated into products which have the potential to result in exposure of consumers. Consumers are defined as people using products that contain D4 outside of the workplace setting. The applicable uses are those in household care products, textile applications, and to a lesser extent, electronics applications. Consumers of these types of products could have the potential for exposure to D4.

Potentially exposed or susceptible subpopulations include pregnant and lactating females and children, as well as subsistence fishermen. Pregnant and lactating females can be exposed via consumer products and general population exposures and nursing infants are potentially exposed to D4 via breastmilk. Potential exposures for children also include contact with infants' and childrens' products (not shown in Figure 4-3).

Section 4.2.1.2.7 summarizes which exposure pathways are considered as part of the Section 5 Exposure Assessment.

Figure 4-3. D4 Human Risk Conceptual Model



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The evaluation of the pathways is described below.

4.2.1.2.1 Air

At MPF facilities, air emissions of D4 may result from air treatment equipment and fugitive emission sources, potentially exposing the general population through ambient air. In addition, volatilization of D4 to ambient air could occur from disposal of MPF facility wastes or consumer products in landfills. These air emissions are airborne vapors that are dispersed in the atmosphere and transported by the wind. During transport, rainfall will not result in deposition of D4 because of the low water solubility, high air/water partition coefficient (thus no wet deposition), and relatively low n-octanol-air partition coefficient (thus insignificant dry deposition) of D4 (Xu 2010). Therefore, the deposition pathway to plants, surface soil, and surface water is an incomplete pathway.

Once emitted to air or volatilized from other media, D4 remains in the air until photo-oxidized. D4 may be inhaled by the general population receptors either at the point of volatilization or downwind of the emission source. This is considered a complete pathway. Consumers that use products containing D4 may be exposed through potential volatilization of D4 in liquids or aerosolization of D4 in products that are sprayed.

4.2.1.2.2 Surface Soil

Sources of emissions to surface soil include land application of sludge resulting from wastewater treatment. During biosolids land application on surface soils, runoff may potentially transport D4 to surface water, but this pathway is considered minor because of the low solubility and high organic carbon-water partition coefficient of D4. From surface soils, D4 is unlikely to infiltrate into the ground water, but may be eroded by wind or volatilized and transported to air. Infiltration and migration into ground water and from ground water to surface water are minimized by the high adsorption to organic carbon and low solubility of D4, which would limit migration from soil to ground water. As a result, the pathways related to ground water are considered incomplete (not shown).

The exposure of the general population to air as a result of volatilization from surface soil is considered complete, given the elevated Henry's Law Constant for D4. Pathways via direct exposure to surface soil via ingestion or direct contact are considered minor, because of the rapid degradation of D4 in soil under dry conditions and rapid volatilization under wet conditions. The potential for uptake from soil by food items (e.g., crops) is considered as a potential exposure pathway for the general population, although this also is a minor pathway due to the lack of biomagnification of D4 in the food chain.

4.2.1.2.3 Surface Water

Sources of emissions to surface water are on-site wastewater treatment plants, municipal wastewater treatment plants, or stormwater runoff from process equipment. Consumer uses can also result in "down the drain" discharges going to WWTPs. Because of the low water solubility of D4 and rapid volatilization and adsorption to sediments, uptake from, or direct contact with surface water by humans are considered incomplete pathways. However, ingestion of drinking water, for which surface water serves as a surrogate, is considered a potential exposure pathway for the general population. In addition, surface water (directly or via transport to sediment) can serve as a pathway for ingestion and contact exposure by fish, which can then be ingested by humans. Due to the low water solubility and high volatility of D4, these ingestion pathways for humans (water and fish ingestion) are considered minor pathways. Volatilization to air from surface water and subsequent exposure of human receptors is considered a complete pathway.

4.2.1.2.4 Sediments

Because D4 is relatively persistent in sediments in standard laboratory studies, uptake of D4 through contact with D4 in sediments is considered a direct pathway for aquatic plants, benthic invertebrates, and fish. In addition, fish may be exposed to D4 via ingestion of benthic food, Exposure for these receptors is addressed in Section 5-2. Exposure of human receptors to D4 in sediments via the food chain (i.e., by ingesting fish) is considered a minor pathway due to the lack of biomagnification of D4.

4.2.1.2.5 Landfills to Air and Ground Water

Solid wastes may be disposed of in landfills, where D4 may volatilize into the air. These solids wastes include those generated from manufacturing operations, activated carbon sent to off-site waste management facilities, and wastes from sludge treatment. This is a complete pathway for exposure of the general population to ambient air. As previously indicated, infiltration of D4 into the ground water is unlikely because of the high soil-water partition coefficient and low solubility, and is considered to be an incomplete pathway (not shown).

4.2.1.2.6 Use of Consumer Products

When using consumer products containing D4, exposure via inhalation is possible from volatilization of D4 directly from liquids or other dermally-applied products or from aerosolization of a sprayed product that contains D4. For potentially exposed or susceptible subpopulations (e.g., infants and very young children), potential exposure through mouthing of children's products is also considered to be a minor pathway (not shown).

4.2.1.2.7 Summary of Exposures for the General Population and Consumers

For the general population, exposure to D4 *through the environment* is considered for the following pathways:

- Inhalation exposure resulting from dispersion in ambient and indoor air
- Ingestion exposure via consumption of food items grown on soil containing D4
- Ingestion exposure via drinking water (surface water serves as surrogate)
- Ingestion of surface soil
- Ingestion exposure via consumption of fish exposed to surface water or sediment containing D4
- Susceptible subpopulation exposure through subsistence fishing
- Susceptible subpopulation exposure through ingestion of breastmilk

For consumers, exposure to D4 *through use of consumer products* is considered for the following pathways:

- Inhalation exposure resulting from potential volatilization and aerosolization following product use
- Dermal exposure from direct contact with products
- Susceptible subpopulation exposure through mouthing of children's products

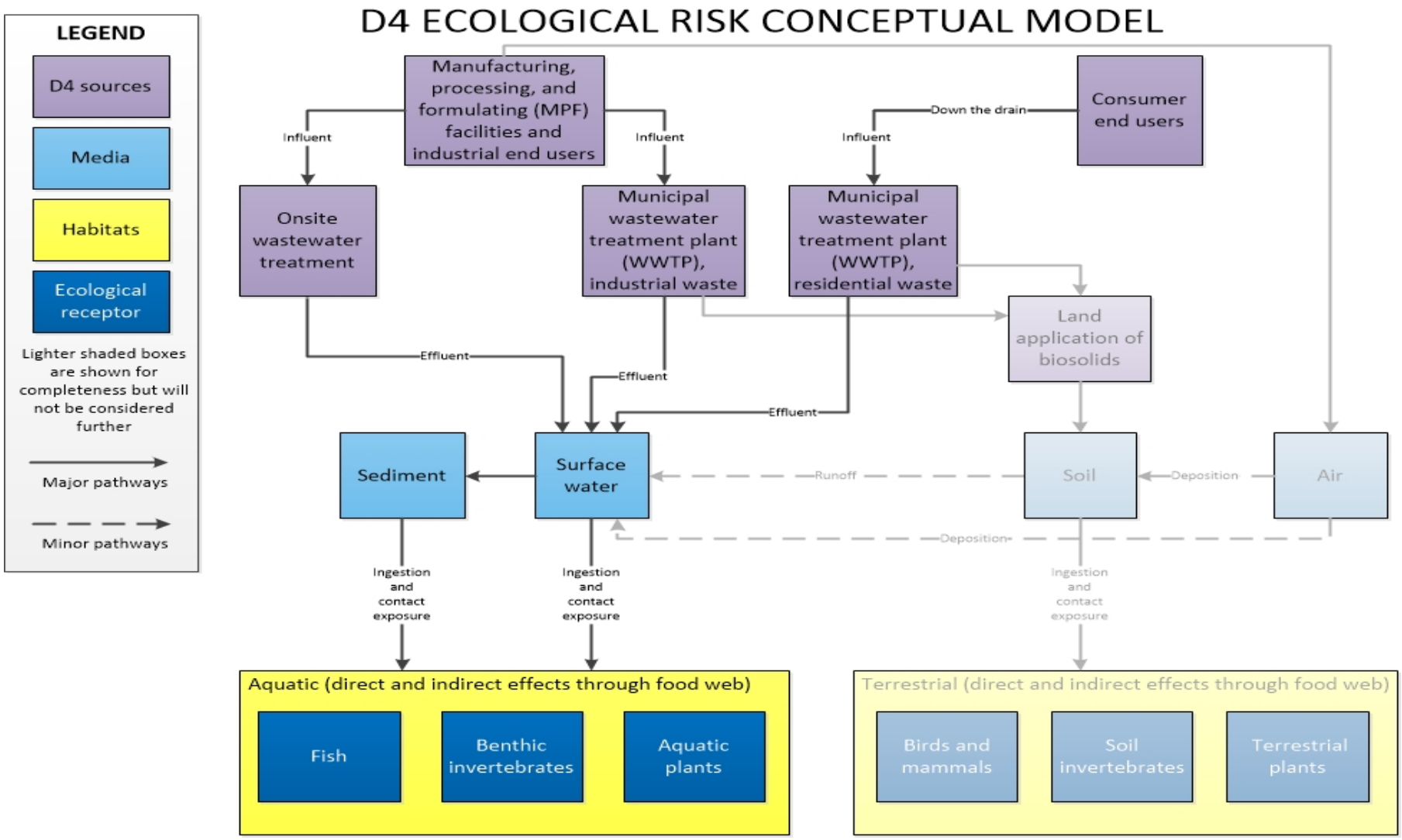
The Exposure Assessment evaluates all the above exposure pathways, with Section 5.1.4.4 identifying which ones are carried through into the Risk Characterization.

4.2.2 Ecological Receptors

The Conceptual Model for ecological receptors is shown in Figure 4-4. Releases of D4 to air are not expected to result in an important pathway for ecological receptors because these species live outdoors where volatile substance such as D4 dissipate rapidly, thus the concentrations available to be inhaled are insignificant. Subsequent deposition of D4 to surface waters and soils is negligible based on the environmental fate profile of D4; this is because D4 has low water solubility, high air-water partitioning, and a relatively low n-octanol-air partition coefficient. Potential exposures from land applications of biosolids are expected to be low due to the high binding coefficient of D4 to soil carbon and its inherent volatility.

The major pathway for potential exposure of ecological receptors is via discharge of aqueous effluent, either from on-site wastewater treatment at MPF facilities or from municipal treatment plants. Relevant exposures for ecological receptors include direct contact and uptake of D4 for aquatic receptors in the water column and/or in sediment, and indirect exposures through the food chain. Exposures of terrestrial organisms are not considered, as these would be expected to be much less than aquatic exposures given how D4 is produced and used, and its environmental fate properties, as described above. Section 5.2 provides further discussion regarding ecological exposures and receptors.

Figure 4-4. D4 Ecological Risk Conceptual Model



4.3 Analysis Plan

The Conceptual Models presented in Section 4.2 illustrate the potential exposures of humans and the environment to D4. The media for potential worker exposure are air, contact with D4 during manufacturing/processing/formulation, and dermal contact with materials containing D4. The media for potential exposure of consumer and general population human receptors includes air, drinking water, soil, food grown in soil containing D4, fish tissue, breastmilk, and products containing D4. The media for potential exposure for ecological receptors includes ambient surface water and sediment, and subsequent food chain exposures. The sources of information for each of these media and the approach for use of the information are discussed below.

As clarification, the consumer and general population exposure assessments for this Risk Evaluation rely primarily on that of Gentry et al. (2017) which in turn was based on that conducted by SEHSC (2008b; also referred to as the Canadian Assessment). Updates to SEHSC (2008b) were made as part of this Risk Evaluation, using more recent information where available. The updated SEHSC (2008b) assessment is referred to as the Updated Assessment. The results from both the Canadian Assessment and the Updated Assessment are included in this Risk Evaluation to demonstrate that the inclusion of new information would not change the results of the Canadian Assessment, nor the Gentry et al 2017 evaluation. The ecological assessment was performed specifically for the D4 Risk Evaluation.

4.3.1 Air

Both indoor and outdoor air concentration values were used to estimate inhalation exposure in this assessment. Contribution from volatilized D4 related to use of dermally applied soothing vapor rub was assessed in SEHSC (2008b) (and Gentry et al. 2017) but excluded from the Updated Assessment because it was considered a personal care product. Indoor air concentration values were based on a survey of D4 in indoor air from homes in Northern Italy. SEHSC (2008b) outdoor air concentration values were taken from surveys of D4 concentrations in Nordic environments. In the Updated Assessment, values from U.S.-based indoor and outdoor surveys were used.

4.3.2 Drinking Water

Humans may be exposed to D4 in drinking water. In the absence of data on D4 concentrations in drinking water, concentrations in surface water can be used. Concentrations in surface water are expected to provide conservative estimates, because additional removal of D4 could potentially occur during the drinking water treatment process. For the Canadian Assessment, average measured values from Kaj et al. 2005 were used. For the Updated Assessment, the monitoring program conducted under the Enforceable Consent Agreement (ECA; U.S. EPA 2014; SEHSC 2016a) provides data on D4 concentrations measured in ambient surface water downstream of MPF sites where there was on-site treatment ("OT sites"), downstream of WWTPs receiving industrial waste from MPF facilities, and downstream of WWTPs receiving primarily domestic waste. Although these data were used to evaluate exposure to ecological receptors, they can provide a conservative estimate of exposure concentrations in drinking water for human receptors. This is because the samples were collected from the mixing zone where discharges of permitted substances are allowed, and thus would likely be higher in concentration than samples collected from actual drinking water intake areas. Also, drinking water treatment processes can remove substances prior to entry into the distribution system. The methods for collection and analysis of samples under the ECA program are discussed in Nusz et al. 2018. Four OT sites were monitored when effluent flow rates were representative of normal plant operations. Five WWTP sites were monitored that were receiving indirect[10] discharge from D4 processors and/or formulators (i.e., D4 reasonably expected in the influent and referred to hereafter as "industrial sites"), as documented through industrial user surveys and other information sources. Five other municipal WWTP sites selected for monitoring were representative of locations that receive less than 15% of wastewater from industrial sources and no wastewater from D4 manufacturing or processing (including product formulation) sites, referred to hereafter as "residential sites." Additionally, for both the residential and industrial dischargers, sites were selected with large discharge rates relative to the receiving body flow rate (low dilution). These sites had activated sludge treatment with secondary clarification and/or disinfection; however, additional forms of treatment were not allowed. A widespread,

[10] Indirect meaning discharge from manufacturer/processor/formulator facilities that do not have on-site treatment. Direct dischargers have onsite wastewater treatment plants and discharge pursuant to their own permits in lieu of sending effluent to a municipal WWTP

geographic representation was also a selection criterion for the sites. The industrial and residential sites were assumed to be representative of the 15,000 to 20,000 municipal WWTPs in the continental United States.

The ECA environmental samples were collected twice at each of the 14 sites, at least three months apart (all events occurred between April 21, 2016, and December 15, 2016) during low-flow months of the receiving waters. Samples were taken during typical weather conditions and at least three days after a high flow weather event such as a heavy rainstorm. Surface water (as well as sediment and biota) were collected during both sampling events at all sites. Samples were collected as close as reasonably possible to the effluent outfall, within the mixing zone. Collection of the surface water followed standard EPA collection methods and included the collection of seven grab samples per event at each location. Of these seven grab samples, three samples were investigative samples from each event and location; other samples were collected and analyzed for quality assurance (QA) purposes. All laboratory analyses were conducted by ALS Environmental laboratory (Kelso, Washington) according to TSCA GLP Standards (40 CFR 792) and the laboratory's standard operating procedures (SOPs). Further details can be found in Section 5.2.

4.3.3 Food

Uptake of D4 by crops grown in soil which are then consumed by humans provides a potential route of exposure. The SEHSC assessment (SEHSC 2008b) relied on the predicted concentrations of D4 in food from agricultural uptake presented in the environmental risk assessment from Brooke et al. (2009). These food types included: fish, meat (assumed to include poultry), plant leaves, root crops, and milk. The SEHSC assessment also provided a discussion on the expected contribution of residual silicone antifoams used in food processing to ingestion exposure. However, there was limited information regarding actual concentrations. Although food processing antifoam products are also considered in the Updated Assessment, they are considered to be under the purview of FDA and technically, should be excluded. However, as discussed in Section 5.1, a number of non TSCA-relevant sources of exposure were conservatively included in this Risk Evaluation.

4.3.4 Soil

Incidental ingestion of soil containing D4 by children and adults can result in potential exposure, although this pathway is considered minor. The distribution of concentrations of D4 found in soil was taken from various reports (discussed in the SEHSC assessment) and, for comparative purposes, environmental data from recent studies (Wang et al. 2013b) were used in the Updated Assessment.

4.3.5 Fish Tissue

Consumption of fish containing D4 is a potential exposure pathway for the general population. In the Canadian Assessment, a most likely value of 0.034 mgkg in food was used. For the Updated Assessment, data were based on fish sampled during the ECA monitoring program at the same times and locations as described in Section 4.3.2. Six investigative samples were collected (three samples, two from each species, if practicable, from different trophic guilds), along with QA samples. Techniques included common seine nets, backpack or boat-mounted electroshocking, gill nets, fyke or hoop nets, and/or rod and reel angling, following methods provided by EPA (U.S. EPA 2003a, 2011a), Powell and Woodburn (2009), and (Zale et al. 2012). Fish were measured (total length) and weighed (wet weight), and a subset at each site was composited for laboratory analysis of D4 to reach a minimum mass of 50 g. Data on concentrations in fish tissue were used to assess exposure of the general population to D4 through this pathway. A lognormal distribution from these data provided a value of 0.0596 mg/kg, on the same order of magnitude as the most likely value used in the Canadian Assessment. These data were also used in the ecological risk characterization by comparison to the threshold for the CTLBB.

4.3.6 Breast Milk

Although this is a minor route of exposure, maternal exposure via general population exposures or consumer products can potentially result in exposure to lactating infants. D4 was only detected in a few samples of breast milk from the study (Hanssen et al. 2013; Kaj et al. 2005) referenced by SEHSC (2008b). It was also noted that the methodology used may have "compromised the integrity of the study samples in which D4 was detected." SEHSC

commented in the submission to Health Canada that “As a result, the validity of the results has been called into question.” No new data were found for the Updated Assessment.

4.3.7 Products Containing D4

Consumers could be exposed through dermal contact to products containing silicones that may contain residual D4. The particular susceptible subpopulation of concern for products containing D4 are infants and young children who could be exposed through mouthing of children’s products. Data for these products were obtained from experimental studies that evaluated the concentration of D4 in various silicone-based products. While product data for dermal contact were not changed in the Updated Assessment, new data relevant to mouthing were used.

4.3.8 Surface Water

Aquatic ecological receptors can potentially be exposed to D4 in surface water. For the environmental risk characterization conducted as part of the D4 Risk Evaluation, data are available on surface water concentrations from the ECA monitoring program, as discussed in Section 4.3.2. These data were used to estimate exposures to aquatic ecological receptors.

4.3.9 Sediment

Aquatic ecological receptors can also be potentially exposed to D4 in sediment. Concurrent with the sampling of surface water in the ECA monitoring program (discussed in Section 4.3.2), sediment samples were collected at points near the surface water collection sites, except at sites devoid of fine-grained sediment where collections were made as close to the water sampling locations as possible, and still within the mixing zone. Three investigative samples were collected per sampling event, at each location, along with QA samples. As with the surface water samples, laboratory analyses were conducted by ALS Environmental laboratory (Kelso, Washington) according to TSCA GLP Standards (40 CFR 792) and the laboratory's SOPs. Data from this sampling program were used to estimate concentrations of D4 in sediment to which benthic organisms might be exposed.

4.3.10 Benthic Invertebrates

As part of the ECA monitoring program, benthic invertebrates were collected at the same sites and locations as the sediment samples. Three investigative samples per event, at each location, along with QA samples, were collected using Ponar dredging and D-frame kick netting or debris picking and sediment vacuum pumps according to techniques provided by Powell and Woodburn (2009) and EPA (U.S. EPA 2003b). When necessary to obtain sufficient biomass, collection of benthic organisms continued at alternate locations within the depositional zone (but not beyond 200 m from the effluent outfall) until sufficient mass was obtained. Taxa were counted and identified to the lowest practicable taxon prior to chemical analysis. The results of the taxonomic analyses are used in an assessment of benthic community metrics in the ecological risk characterization (Section 7.2).

4.3.11 Worker Exposure Data

Workers are potentially exposed via inhalation and dermal routes of entry during D4-related manufacturing, formulation, and processing. Worker inhalation monitoring (personal sampling) is available for manufacturing and processing operations (SEHSC 2019) and data from personal sampling were used in assessment of risk to workers. Additional data on worker inhalation exposures during manufacturing is available from Gentry et al. 2017. For potential exposures by office workers (inhalation) and barbers / beauticians (inhalation and dermal), information was obtained from Gentry et al. 2017.

5 Exposure Assessment

5.1 Human Health Exposure Assessment

This section presents the approach for a human health (worker, consumer, and general population) exposure assessment of D4. The approach used in the exposure assessment incorporates the expected requirements in the Final Rule (*Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Ac*t 82 Fed. Reg. 33726; U.S. EPA 2017b). The exposures are based on the conceptual models of D4 worker, consumer, and general population exposure pathways as discussed in Section 4.2.1. Key sources of information used for the human health exposure assessment are presented in this section.

The goal of the human health exposure assessment is to assess and quantify potential exposure to workers, consumers, and the general population, including potentially exposed or susceptible subpopulations such as infants, children and women of childbearing age, as well as subsistence fisherman populations.

The worker exposure assessment is based on personal worker exposure monitoring conducted by SEHSC member companies during manufacturing and processing activities (SEHSC 2019). Additional information on worker exposure is also provided in Gentry et al. (2017), which includes TSCA relevant exposure (D4 manufacturing) and TSCA non-relevant exposure (formulation of personal care products and worker exposures for barbers and beauticians and office workers). The TSCA definition of “chemical substance” excludes any food, food additive, drug, cosmetic or device as defined under the Federal Food, Drug, and Cosmetic Act when manufactured, processed, or distributed in commerce for use as such. 15 U.S.C. 2602(2). Therefore, the manufacture, process, distribution and use of a chemical in those applications is not regulated under TSCA. For example, with respect to personal care products, the FDA would typically have jurisdiction, whereas worker exposure to these personal care products during their formulation is regulated by the Occupational Safety and Health Administration (OSHA). However, exposures based on the formulation of skin care products was used as a conservative and sentinel estimate for all worker exposure. This worker exposure assessment also includes

the conversion of the worker exposures from Gentry et al. (2017), including both TSCA relevant and TSCA non-relevant exposures, to human internal dose levels by physiologically based pharmacokinetic (PBPK) modeling. Conversion of exposures to human internal dose levels was necessary to permit direct comparison in the same units of the exposures to the derived Point of Departure (POD) for risk characterization, which was also derived by PBPK modeling. Because human internal dose levels include all TSCA-relevant and TSCA non-relevant exposures, this approach provides a conservative estimate of worker exposure.

The consumer and general population exposure assessments conducted by Gentry et al. (2017) are presented. Monte Carlo analysis was used to determine exposures for these groups. Gentry et al. (2017) used the same data from consumer and general population human health exposure assessments conducted by SEHSC (2008b) for Health Canada (discussed below), which includes TSCA-relevant as well as TSCA non-relevant exposures. As above with worker exposure, the results of consumer and general population exposures, including both TSCA relevant and TSCA non-relevant exposures, were converted to human internal dose levels by PBPK modeling. Conversion of exposures to human internal dose levels was necessary to permit direct comparison in the same units of the exposures to the derived POD for risk characterization, which was also derived by PBPK modeling. Because human internal dose levels include all TSCA-relevant and TSCA non-relevant exposures, this approach provides a conservative estimate of consumer and general population exposures.

This section also reviews the combined consumer and general population human health exposure assessments conducted by SEHSC (2008b) for Health Canada, the Canadian Assessment. The Canadian Assessment includes TSCA-relevant exposures as well as non-TSCA relevant exposure (personal care products, cosmetics, food contact materials and OTC medications) that are regulated by FDA and are therefore exempt from TSCA. Gentry et al. (2017) also uses the same data from the Canadian Assessment and therefore also includes both TSCA-relevant and non-relevant exposure assessments. For transparency, the exposure evaluation here presents results from the Canadian Assessment as well as an updated TSCA-relevant exposure assessment. The updated TSCA-relevant exposure assessment excludes non-

TSCA relevant exposures (except as noted) and includes any information newly available in publicly available literature and references (post-2008).

5.1.1 Worker Exposure Assessment

The Conceptual Model for exposure of workers is shown in Section 4.2.2.1 and includes worker exposure (inhalation and dermal) during the manufacture of D4, processing of D4, and the formulation of products containing D4, as well as non-TSCA related exposures by office workers (inhalation) and barbers / beauticians (inhalation and dermal).

5.1.1.1 Applicable Routes of Exposure

5.1.1.1.1 Oral Exposures

Oral exposures are not relevant to workers (Gentry et al. 2017).

5.1.1.1.2 Dermal Exposures

Gentry et al. (2017) prioritized worker exposures that would present the greatest potential for intake. Based on the human internal dose levels obtained through PBPK modeling, which include a dermal absorption value of 0.5%, Gentry et al. (2017) concluded that dermal exposure was not significant for TSCA-relevant worker exposures (manufacturing, formulation, and processing of TSCA-relevant and non-relevant products). This determination for the exclusion of dermal pathways for TSCA relevant exposure is supported by the low dermal absorption potential of D4 and by the manufacturing and processing of D4 in closed systems. Furthermore, for any potential dermal contact, worker exposures are mitigated through the required use of impervious gloves, uniforms (e.g., long pants/long sleeve shirt/closed toe shoes), and safety glasses.

However, Gentry et al. (2017) concluded that barbers and beauticians had the potential for dermal intake through the application of haircare products containing D4. Although personal care products are regulated by the FDA, worker exposure is regulated by OSHA, and dermal exposures by barbers and beauticians is not relevant under TSCA, this pathway is included to provide a conservative worker assessment.

5.1.1.1.3 Inhalation Exposure

Gentry et al. (2017) determined that inhalation was the only applicable route of exposure for TSCA-relevant workers; i.e. workers involved in the manufacture of D4 based on the information provided by Maxim (1998). Non-TSCA relevant inhalation exposures identified by Gentry et al. (2017) include formulation of personal care products, barber and beautician exposures, and office worker exposure. Formulation of personal care products was used as a conservative estimate for TSCA-relevant formulation of products (e.g., household care).

It is important to note, that in addition to general ventilation and engineering controls used to reduce airborne TSCA-relevant exposures to D4, any potential worker exposures that are expected to be at or above the workplace environmental exposure level (WEEL®) value, 8-hour TWA of 10 ppm (121,320 µg/m^3, OARS WEEL 2017), are mitigated by the required use of air purifying respirators. Because D4 is an existing chemical under TSCA, with existing global hazard classification and risk evaluations, the use of respirators is required and is in place globally for exposures above the TWA.

5.1.1.2 Manufacturer and Processor Worker Exposure

The manufacture and processing of D4 are conducted in closed systems. Worker monitoring (personal air sampling) for all potential manufacturing and processing exposures has been conducted by SEHSC members (SEHSC 2019). The results of worker monitoring are summarized below as the maximum concentration in air reported for each category:

- chemical operators: all samples results < 1 ppm, except as noted:
    - 1.2 ppm [D4 loading to vessel] 480 minutes per day, every week, for 50 weeks
    - 1.4 ppm [process sample collection] duration of exposure for sampling is up to 30 minutes per day (15 minutes per day up to twice per day)
    - 12 ppm [process filter change (workers use full air purifying respirators for this activity)] estimated duration of exposure 15-30 minutes, estimated to occur a maximum of once a week for 50 weeks
- lab technicians: not detectable (0.04 ppm)
- logistics operator: all sample results < 1 ppm

As stated above, any potential exposures at or above 10 ppm (WEEL® value, e.g., during process filter changes) are mitigated using impervious gloves, uniform (e.g., long pants/long sleeve shirt/closed toe shoes), safety glasses, and full air-purifying respirators. Because D4 is an

existing chemical under TSCA, with existing global hazard classification and risk evaluations, the use of respirators is required and is in place globally for exposures above the TWA. The worker exposure value was therefore based on potential worker exposures that *do not* require the mandatory use of a full-air purifying respirator.

The results of air monitoring performed by SEHSC member companies are not included in this analysis as the focus is individual worker exposure to D4. Gentry et al. (2017) states that the average D4 air concentration measure in the workplace for workers involved in the manufacture of D4 is 0.1908 ppm (2310 µg/m^3) (Maxim 1998).

Based on the information provided by SEHSC (2019) for personal exposure monitoring for manufacturing and processing activities, the worker exposure (manufacturing and processing) from D4 loading to vessel [1.2 ppm (14,558 µg/m^3)] will be used as a surrogate for all manufacturing and processing worker activities since it reflects the longest potential duration of exposure (480 minutes per day) without required personal protective equipment (PPE) (full-air purifying respirator). This value, based on personal exposure monitoring, is higher than that provided in Gentry et al. (2017) of 0.1908 ppm (based on average air concentrations in the workplace). The SEHSC (2019) air sampling results and those summarized in Gentry et al. (2017) are presented in Table 5-1. Table 5-2 presents the worker inhalation exposure parameters from Gentry et al. (2017).

Based on the information provided by SEHSC from personal exposure monitoring for manufacturing and processing activities (SEHSC 2019), the exposure for process sample collection is 1.4 ppm, but the duration of exposure for sampling only ranges up to 30 minutes/day (15 minutes/day up to twice per day) compared to up to 480 minutes a day for loading to vessel.

There is an additional short-term exposure to higher levels of D4 (up to 12 ppm) during the process of filter changes. Filter changes are estimated to require 15-30 minutes of exposure, and to occur a maximum of once a week for 50 weeks per year.

Based on the above information, the worker exposure (manufacturing and processing) from D4 loading to vessel of 1.2 ppm (14,558 µg/m3) is identified as a surrogate for all manufacturing and processing worker activities. However, since internal dose estimates for workers are not available in Gentry et al. 2017 for workers engaged in D4 loading to vessel, the higher and more conservative exposure of 2.44 ppm for workers involved in the formulation of skin care products is used to provide a conservative risk estimate for manufacturing/processing workers. For skin care formulators, the internal dose levels based on PBPK modeling are: 1.44×10^{-1} mg-hr/L blood/day in men and 7.88×10^{-2} mg-hr/L blood/day in women (Table 5-3).

5.1.1.3 Formulation Worker Exposure

Under TSCA, formulation of industrial and consumer products containing D4 is relevant to this exposure assessment. SEHSC (2019) did not include personal exposure monitoring via formulation of industrial and consumer products. As stated above, Gentry et al. (2017) determined that inhalation was the only applicable route of exposure for workers involved in the formulation of D4 products (TSCA relevant and TSCA non-relevant).

The inhalation exposure information presented in Gentry et al. (2017) for the formulation of personal care products, based on the information reported by Maxim (1998), is used as a conservative estimate for all TSCA-relevant worker exposures. The most conservative inhalation exposure estimate for formulation is 2.44 ppm (29,600 µg/m^3), based on workers involved in the formulation of skin care products. Formulation inhalation exposures are presented in Table 5-2. The maximum internal dose levels based on PBPK modeling are for skin care product formulators: 1.44×10^{-1} mg-hr/L blood/day in men and 7.88×10^{-2} mg-hr/L blood/day in women (Table 5-3).

5.1.1.4 Additional TSCA Non-Relevant Worker Exposure

Gentry et al. (2017) provides dermal exposure values for barbers and beauticians. These authors determined a conservative (maximal) estimate of exposure based on 12-15 exposures during a given work day to a single product that would provide the largest exposure to D4. The maximal dermal exposure to barbers and beauticians is 14.1 mg of D4 exposure per application. The internal dose levels based on dermal exposure and PBPK modeling were 8.98×10^{-4} mg-hr/L

blood/day for men and 2.16×10^{-3} mg-hr/L blood/day for women after 5 days of work and 1.14×10^{-3} mg-hr/L blood/day for men and 2.73×10^{-3} mg-hr/L blood/day for women after 4 days of work (Table 5-3).

Inhalation exposure for formulation of TSCA non-relevant products was discussed in the previous section. Gentry et al. (2017) provided inhalation exposures for barbers and beauticians (0.085 ppm or 1000 µg/m^3) (Table 5-2). The internal dose levels based on PBPK models to barbers and beauticians were 3.63×10^{-3} mg-hr/L blood/day in men and 2.03×10^{-3} mg-hr/L blood/day in women after 5 days of work and 3.60×10^{-3} mg-hr/L blood/day in men and 2.01×10^{-3} mg-hr/L blood/day in women after 4 days of work; these data are presented in Table 5-3.

Gentry et al. (2017) provided two inhalation exposure estimates for office workers, 0.000383 ppm (5 µg/m^3) and 0.000781 ppm (10.2 µg/m^3) (Table 5-2). The internal dose levels based on inhalation exposure and PBPK modeling for office workers were 2.26×10^{-5} mg-hr/L blood/day in men and 1.24×10^{-5} mg-hr/L blood/day based on 0.000383 ppm exposure and 4.61×10^{-4} mg-hr/L blood/day in men and 2.50×10^{-5} mg-hr/L blood/day in women based on 0.000781 ppm exposure (Table 5-3).

5.1.1.5 Summary: Worker Exposure

The results of the SEHSC (2019) personal exposure monitoring data provide a conservative exposure of 1.2 ppm (14,558 µg/m^3), for manufacturing and processing of D4 compared to the air concentration estimate for worker exposure used by Gentry et al. (2017) of 0.1908 ppm (2310 µg/m^3). However, internal dose estimates are not available for these workers. Thus, the internal doses for skin care formulators, based on an exposure of 2.44 ppm, are used as a surrogate. Since personal exposure monitoring data are not available for the formulation of occupational or consumer products containing D4, exposure data (0.12 to 2.44 ppm) and internal dose estimates for workers engaged in the formulation of various personal care products are used.

Table 5-3 and Table 5-4 present the internal doses for worker exposures (based on exposures in Table 5-2). Conversion of exposures to human internal dose levels was necessary to permit

direct comparison in the same units of the exposures to the derived POD for risk assessment, which was also derived by PBPK modeling. Because human internal dose levels include all TSCA-relevant and TSCA non-relevant exposures, this approach provides a very conservative estimate of worker exposures. The internal doses for worker exposure provided in Table 5-3 are used in the current risk characterization and Table 5-4 summarizes the key exposure and internal dose metrics for workers.

5.1.2 Overview of Consumer Exposure Assessment Conducted by Gentry et al. (2017)

Gentry et al. (2017) first performed a series of Monte Carlo analyses to prioritize the consumer pathways that would potentially result in the greatest exposure. Only those scenarios associated with the greatest exposure were included in the PBPK analysis. Gentry el et al. (2017) stated that the Monte Carlo analysis produced a distribution of estimates of the intake of D4 in mg/kg of body weight (bw)/day for each consumer product using distributions for the parameters in order to identify those exposure scenarios that provided the greatest potential for exposure to D4. Only those exposure pathways associated with specific product usage that had the largest mean and upper bound estimates for intake, based on the results of the Monte Carlo analysis, were then used for the PBPK analysis to obtain an estimate of the internal dose for comparison to the internal dose associated with the POD.

The exact equations and parameters used to assess each population and exposure pathway were included in Gentry et al. (2017) and the supplemental tables in the Supplemental Information document.

5.1.2.1 Applicable Routes of Exposure (Gentry et al. 2017)

5.1.2.1.1 Oral Exposure

Oral exposure to consumer products was limited to ingestion of lipstick, which was incorporated in the overall oral exposure estimate in the general population PBPK model. Gentry et al. (2017) concluded oral exposures to consumer products was largely incidental and not a major exposure pathway of concern.

5.1.2.1.2 Dermal and Inhalation Exposure

For consumer exposures, personal care products and OTC medication (vapor rub) are TSCA non-relevant exposures. The aggregated dermal and inhalation exposure from application of personal care products (which includes these sources) was used as a surrogate for household cleaners.

5.1.2.2 Consumer Exposure Assessment Methods (Gentry et al. 2017)

Gentry et al. (2017) "determined from the Monte Carlo analysis that in all cases, specific personal care product use (body lotion, hair spray, foundation, after shave and AP (antiperspirants) by adults provided the highest contribution to potential D4 exposure. For example, estimates of intake for the remaining consumer products (for adults, male and female) were 33% or less than the estimated intake of D4 from use of body lotion in adult females. These results demonstrate that it is not likely that consumer products beyond these products would represent a significant contribution to the potential exposure to D4."

Therefore, the PBPK analysis for personal care products conducted by Gentry et al. (2017) was limited to the products identified as contributing the most to potential consumer exposure based on the Monte Carlo analysis results. This approach identified the largest potential contributors to exposure and with application of the PBPK model provides the estimated internal dose metrics associated with exposure to these products.

Gentry et al. (2017) included the following key considerations in estimating internal dose metrics associated with dermal exposure from the use of consumer products: the amount of D4 in the product, the amount applied, the surface area over which the product was applied, and the frequency of the application (Table 5-5 and Table 5-6).

For consumer inhalation exposure, the PBPK modeling was conducted using air concentration data that were available for selected consumer products as reported in Gentry et al. (Table 5-7).

As the current PBPK model (McMullin et al. 2016) is not designed to estimate internal dose metrics for children, child scenarios were qualitatively related to the PBPK results from adult scenarios evaluated in the PBPK analysis in Gentry et al. (2017).

5.1.2.3 Consumer Exposure Results (Gentry et al. 2017)

The values used in the Gentry et al. (2017) risk characterization were the internal dose metrics calculated from PBPK modeling for consumer products as presented in Table 5-8 and the corresponding 95th percentile exposures in mg/kg bw/day are presented in Table 5-10. The highest internal dose in men and women from dermal exposure was based on hand/body lotion exposure. 2.49×10^{-3} mg-hr/L blood/day in men and 3.14×10^{-3} mg-hr/L blood/day in women). The highest internal dose in men and women from inhalation exposure was from roll-on deodorant (2.04×10^{-3} mg-hr/L blood/day in men and 2.31×10^{-3} mg-hr/L blood/day in women).

5.1.2.4 Summary: Consumer Exposure (Gentry et al. 2017)

All results from the evaluation of dermal and inhalation exposure to consumer products, specifically those personal care products included in Gentry et al. (2017), are considered conservative overestimates of exposure for the current Risk Evaluation. All of the personal care products would be considered FDA-regulated products and would therefore fall outside the purview of consideration for a submission to EPA. However, these values are used as surrogates for exposure to TSCA relevant consumer products (e.g., household care products). Additionally, consumer exposure values for personal care products used by Gentry et al. (2017) are conservative due to the decreasing concentrations of D4 in personal care products over the past 20 years (Gentry et al. 2017). With the exception of ingestion of lipstick (which was considered as part of the ingestion pathway of food, water, and soil to the general public), oral exposure to consumer products is largely incidental and not a major exposure pathway of concern.

5.1.3 Overview of General Population Exposure Assessment Conducted by Gentry et al. (2017)

General population exposures in Gentry et al. (2017) included indoor and outdoor air, as well as the ingestion of D4 from drinking water, food, breast milk, and soil, and mouthing of consumer products by children (e.g., pacifiers, infant toys) for general population.

Gentry et al. (2017) first performed a series of Monte Carlo analyses to prioritize the general population pathways that would potentially result in the greatest exposure. Only those scenarios associated with the greatest exposure were included in the PBPK analysis. Gentry et al. (2017) stated that the Monte Carlo analysis produced a distribution of estimates from general sources (air, water, food and soil) using distributions for the parameters in order to identify those exposure scenarios for the exposure pathways that provided the greatest potential for exposure to D4. Only those exposure pathways associated with specific product usage that had the largest mean and upper bound estimates for intake, based on the results of the Monte Carlo analysis, were then used for the PBPK analysis to obtain an estimate of the internal dose for comparison to the internal dose associated with the POD.

The exact equations and parameters used to assess each population and exposure pathway were included in Gentry et al. (2017) and the supplemental tables in the Supplemental Information document.

5.1.3.1 Applicable Routes of Exposure (Gentry et al. 2017)

Relevant exposures as determined by Gentry et al. (2017) include foods, food additives and food contact materials, cosmetics, infant products (bottle nipples, sipper cups and straws), and OTC medical products (anti-gas medication).

For the oral exposure estimate, the authors used the mean and 90th percentile results (in mg D4/kg-body weight/day) from the Monte Carlo analysis that combined multiple sources of oral exposure, including food, water, soil, residual antifoam, and lipstick. Estimates for exposure of children to D4 using silicone rubber products, such as teethers or sippy cups, is dependent on the migration rate of the siloxanes from the product into saliva or other fluids. Migration tests

were performed using silicone cake pans, which was demonstrated to be an appropriate surrogate. These cake pans had an average concentration of D4 of 23 mg/kg (Zhang et. al., 2012). Migration from food containers was assumed to be an amount per day over the duration of exposure, but there is little evidence that this amount could be repeatedly extracted from the same product each day or that a new product would be used each day. Therefore, this is a very conservative estimate of the daily exposure and would result in an overestimation of D4 exposure. Oral exposure to the general public from environmental media or to subsistence fisherman were not carried further in the risk evaluation because the exposure potential was determined to be two times less than the product representing the greatest exposure to D4 through consumer use (e.g., body lotion for adults).

Dermal exposure to the general population was not considered a pathway of concern in Gentry et al. (2017). Based on the results of the Monte Carlo analysis performed by Gentry et al. (2017), dermal exposure was not considered to impact the exposure assessment for the general population. This is supported by the low dermal absorption rate of D4 (0.5%), thus limiting the potential for dermal exposure to the general population.

For inhalation exposures among the general population, Gentry et al. (2017) evaluated indoor and outdoor air.

5.1.3.2 General Population Exposure Assessment Methods (Gentry et al. 2017)

The exposure scenarios and values used by Gentry et al. (2017) were the same as that discussed in the Canadian Assessment in Section 5.1.4.1 below. The general population inhalation exposure inputs (in mg D4/kg-body weight/day) for the PBPK model were calculated using point estimates of the parameters with distributions from the Monte Carlo analysis. These included the ‘most-likely’ value from parameters with a triangular distribution, the mid-point for those with a uniform distribution, and the mean value for those with a lognormal or normal distribution. The exact equations and inputs used by these authors are outlined in the publication and in the Supplemental Information document.

The PBPK analysis for the general population considered both inhalation of indoor and outdoor air in the home environment, exposure to D4 in environmental media (e.g. ingestion of water, soil, air, fish, breast milk, and other foods), ingestion of lipstick, ingestion from children's products (sipper tube, baby bottle nipple), and ingestion of anti-gas medication. Exposure to environmental media was also considered for subsistence fishermen where the consumption of fish was assumed to be the main source of protein.

5.1.3.3 General Population Exposure Results (Gentry et al. 2017)

The oral exposure parameters for Monte Carlo analysis are presented in Table 5-9 and the 95th percentile exposures in mg/kg bw/day are presented in Table 5-10. The mean reported oral intake of D4 determined from the Monte Carlo analysis of Gentry et al. (2017) ranged from 0.005 mg/kg/day for males and females ages 60 and older to 0.007 mg/kg/day for male and female subsistence fishermen ages 12 to 19 years of age. The 90th percentile of oral intake to D4 was approximately 0.009 mg/kg/day for males in the general population or subsistence fisherman 20 to 59 years of age. Since general population oral exposures (environmental media, and food including subsistence fishing) were considerably less than the dermal consumer exposures, Gentry et al. 2017 did not carry oral exposures for the general population into their risk characterization and thus did not determine oral internal doses for this population.

The AUCs estimated for inhalation exposure to D4 for the general public ranged from 2.15 × 10^{-6} to 3.8×10^{-6} mg-hr/L blood/day for the female and male receptors, respectively, from exposure to outdoor air (Table 5-12). A range of AUCs of 1.08 ×10^{-4} to 1.9× 10^{-4} mg-hr/L blood/day was estimated for the females and males respectively, from exposure to indoor air. Exposure to the general public from environmental media or to subsistence fisherman were not carried further in the risk evaluation because the exposure potential was determined to be two times less than the product representing the greatest exposure to D4 through consumer use (e.g. body lotion for adults).

The results from the Monte Carlo analysis indicated that oral intakes in children are up to 10 times greater than intakes estimated for adults.

Gentry et al. (2017) considered the general population to be individuals who could be exposed to levels of D4 in outdoor or indoor air for purposes of their assessment.

5.1.3.3.1 Indoor Air

For indoor air "a value of 10 μg/m^3 (0.000766 ppm) D4 in indoor air was identified from the New York Indoor Environmental Quality Center study (NYIEQ, 2005) and was assumed to be representative of the indoor air concentration to which an individual in the general public would be exposed." The general population inhalation exposures used by Gentry et al. (2017) are summarized in Table 5-11 and the internal dose levels based on PBPK modeling are presented in Table 5-12. The internal dose levels used in risk characterization for indoor air were 1.9×10^{-4} mg-hr/L blood/day in men and 1.08×10^{-4} mg-hr/L blood/day in women.

5.1.3.3.2 Outdoor Air

For outdoor air, "a value of 0.2 μg/m^3 (0.0000153 ppm) was identified as representative of the typical exposure to D4 in outdoor air and was used to estimate D4 exposure for the general public. This value was estimated using the average of the median or midpoint of the reported outdoor air concentration ranges from all the available published studies (Boehmer et al. 2001; Kaj et. al. 2005; Norden 2005; Shields et. al. 1996)." The general population inhalation exposures used by Gentry et al. (2017) are summarized in Table 5-11 and the internal dose levels based on PBPK modeling are presented in Table 5-12. The internal dose levels used in risk characterization for indoor air were 3.8×10^{-6} mg-hr/L blood/day in men and 2.15×10^{-6} mg-hr/L blood/day in women.

5.1.3.4 Summary: General Population Exposure (Gentry et al. 2017)

The values used in the risk characterization by Gentry et al. (2017) were the internal dose metrics for general population exposure as presented in Table 5-12. As stated above, oral exposures to the general public from environmental media or to subsistence fisherman were not carried further in the risk evaluation because the exposure potential was determined to be two times less than the exposure representing the greatest exposure to D4 through consumer use (e.g. body lotion for adults). Dermal exposure to the general population was not considered a pathway of concern in Gentry et al. (2017).

As part of this Risk Evaluation, more recent indoor air data were compared to the exposure assessment of Gentry et al. (2017). Concentrations of D4 in indoor air available from Tran and Kannan (2015) who reported on a survey of homes in Albany, New York, were considered. The new value that would be used for the distribution (median = 0.116 µg D4/m^3 air, Table 5-15) is two orders of magnitude lower than that used in Gentry et al. (2017). Therefore, any exposure calculation made using the indoor air concentration reported in Gentry et al. (2017; the basis of this Risk Characterization) would conservatively overestimate an exposure calculation made using the newer Tran and Kannan (2015) value.

For this Risk Evaluation, new data on the concentrations of D4 found in outdoor air from Yucuis et al. (2013), which reported on urban air in Chicago, Illinois, were considered. Updated values that could be used for the distribution (median = 0.054 µg D4/m^3, Table 5-15) were less than one order of magnitude lower than those used by Gentry et al. (2017). Therefore, any exposure calculation made using the outdoor air concentration reported in Gentry et al. (2017; the basis of this Risk Characterization) would conservatively overestimate an exposure calculation made using the newer Yucuis et al. 2013 value.

5.1.4 SEHSC (2008b) and Updated SEHSC Consumer and General Population Exposure Assessments

The consumer and general population exposure assessment for this Risk Evaluation relies primarily on that of Gentry et al. (2017) which in turn was based on that conducted by SEHSC (2008b; the Canadian Assessment). Updates to SEHSC (2008b) were made as part of this Risk Evaluation, using more recent information where available. The updated SEHSC (2008b) assessment is referred to as the Updated Assessment. The results from both the Canadian Assessment and the Updated Assessment are included to demonstrate that the inclusion of new information would not change the results of the Canadian Assessment, nor impact the assessment by Gentry et al. (2017).

5.1.4.1 Canadian Assessment

The Canadian Assessment did not divide exposures into consumers and the general population. The exposure estimates in the Canadian Assessment for each route, as well as an estimate of

cumulative exposure (all routes) for each of the six population groups are provided in Table 5-13 and Table 5-14 (adults and children, respectively; information without highlight; in mg/kg bw/day). Both average and upper bound exposures were estimated. Since exposure to D4 is expected to be chronic, the 90th percentile of exposure was considered an appropriate metric of upper bound exposure.

The Canadian Assessment states that "based on the widespread use of D4 in consumer products, as well as its physico-chemical properties, it is expected that the likelihood of general population exposure is high." The routes of human exposure were estimated by considering the following pathways:

- Inhalation of ambient air and indoor air. In other human health risk assessments for priority chemicals, inhalation of indoor air is expected to capture most exposure from consumer products (per Health Canada's Priority Substance Risk Assessment Guidance Document).
- Ingestion of D4 from drinking water, food, OTC medication (anti-gas medication), breast milk, lip-area cosmetics, consumer products for children (e.g.: soothers) and soil.
- Dermal absorption of D4 from use of consumer products.

In the Canadian Assessment, measured and calculated values for D4 concentrations in environmental media were based on those reported in the UK EA Environmental Risk Assessment (Brooke et al. 2009). As stated in the Canadian Assessment: "To capture likely human exposure and maintain consistency with previous risk assessments, experimental values from this work were selected to model D4 concentration in environmental media. In some cases, only limited or surrogate data were available. For example, no reported measurements of D4 concentrations in drinking water were found. Therefore, data on D4 concentrations in surface water were selected, as surface water is expected to be a reasonable surrogate for drinking water. Experimental measurements of D4 in ambient air, indoor residential air, surface water, and soil referenced in the UK environmental risk assessment were used to support this exposure assessment." Additional details on input parameters for the Canadian exposure assessment are available in SEHSC (2008b; specifically, Tables 3a-j) and provide the details of the data used to develop D4 concentration distributions. These details are not repeated in this document. The results of the Canadian Assessment are summarized below.

Analysis of the various routes of exposure shows that both at the mean and at the 90th percentile, for the adult age groups, ages 12-17 years, 20-59 years and 60+ years, dermal exposure is the primary route by which humans intake D4 (Table 5-13). Dermal exposure is primarily attributable to use of consumer products (personal care products and cosmetics, as surrogate for household care products) that contain D4, contributing about 80% of average exposure for men and about 90% for women.

Cumulative estimates of exposure for children were developed as well (Table 5-14). For children the primary exposure route varies by age group: children 0-6 months and females 4-11 years (ingestion), children 6 months – 4 years and males 4-11 years (dermal).

Exposure estimates were also developed for subsistence populations (Table 5-13 and Table 5-14). These are population groups who depend more heavily on the consumption of fish and shellfish than the general population. Specifically, this analysis suggests that there is potentially slightly higher exposure to D4 for subsistence fishermen. Since the only computational difference in this analysis between the subsistence and general populations is the consumption of fish, it was inferred that consumption of fish and shellfish may have a perceptible impact on D4 exposure.

In conclusion, the Canadian assessment of exposure predicted the cumulative exposure to D4 from inhalation, ingestion, and dermal routes of exposure. Average adult exposures which were around 0.01 mg/kg-bw/d or less are dominated by dermal exposure, via the consumer use of personal care/cosmetic products that may be formulated with D4. At the upper bound, adults' exposures would not likely exceed 0.025 mg/kg-bw/d. Average children's exposures, which were around 0.015 mg/kg-bw/d or lower, are dominated by ingestion or dermal. At the upper bound of exposure, infants' exposures would be less than 0.06 mg/kg-bw/d. Detailed results by each individual route of exposure are given in Table 5-13 and Table 5-14 (rows without highlights).

5.1.4.2 Updated Assessment

An Updated Assessment of exposure based on the Canadian Assessment was conducted to provide clarity on the conservative nature of the Canadian exposure assessment, as well as the information used by Gentry et al. (2017). The Updated Assessment includes relevant information from a systematic literature review conducted to gather information post-2008 (see Section 2), because information up to 2008 was included in the Canadian assessment.

Information from the systematic literature review was used to identify relevant studies post-2008 that contained information related to D4 concentrations in various media. Exposure values were either replaced in the assessment or were checked against existing values to ensure general concordance. If multiple new studies reported concentration values, the most conservative (highest) concentration for each exposure type was used. In addition, uses that were deemed TSCA non-relevant were excluded from the updated assessment where appropriate and feasible. Exposure parameter details are provided below and presented in Table 5-15 through Table 5-20.

Exposure	Updated Assessment Change
Consumer	
	Exposures related to items covered by FDA or EPA Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) regulations were verified, but not updated.
	Dermal exposures from personal care products were not updated and were used as a surrogate for TSCA-relevant consumer products (e.g., household cleaners)
	Oral exposure was not considered for consumer exposure. Oral exposure to consumer products was limited to ingestion of lipstick, which was incorporated in the overall oral exposure estimate in the general population model in the Canadian assessment. Because this is a use that is TSCA non-relevant, it was excluded from the updated assessment
	The OTC products are likewise excluded because the OTC vapor rub products are considered a drug and fall under the purview of FDA.
General Population	
Surface Water - oral	Surface water was used as a surrogate for drinking water. Drinking water has been included as a potential route of exposure. However, based on its physico-chemical properties, the presence of D4 in drinking water is unlikely.
	In the updated assessment, distributions of water intake were obtained from the EPA Exposure Factors Handbook (EFH) (U.S. EPA 2008, 2011c). Updated values were added to reflect the distribution of US-based consumption of tap water for different age groups. There was additional detail for infants <1 year old as it related to breastfeeding status and tap water consumption, which was factored into the exposure estimate for that age group (Table 5-19).
	In the updated assessment, the drinking water values were updated with surface water data from the larger ECA monitoring program (84 samples, Nusz et al., 2018), which reported values (0.03 µg/L, Table 5-16 and Table 5-20) approximately one order of magnitude lower

	than the Predicted Environmental Concentrations (PECs) used in the Canadian assessment. The use of surface water data is conservative because surface water typically undergoes treatment prior to distribution as drinking water.
Soil- oral	In the updated assessment, while soil ingestion is not expected to contribute significantly to overall exposure, there are data available on concentrations of D4 in biosolid amended soil in North America. Wang, et al. (2013b) reported concentrations in biosolid-amended soil between <0.008 and 0.017 µg/g dry weight. The most likely value chosen for the analysis (8 µg/kg soil, Table 5-16 and Table 5-20) was similar to the values reported in the Canadian assessment.
Fish and shellfish- oral	In the updated assessment, the intake distribution for fish in subsistence fisherman populations was updated for children only (Table 5-16). No new data were identified for adult subsistence fisherman populations. Updated, measured concentration data were identified for fish from the ECA monitoring program described in Nusz et al. (2018). The most likely value in the initial analysis of 0.034 mg/kg fish was replaced with a lognormal distribution from new measurement data and a most likely value of 0.0596 mg/kg fish (Table 5-16 and Table 5-20). This value was on the same order of magnitude as the most likely value used in the original assessment.
Children's products- oral	Infant bottle nipples /sipper tubes/straws (all considered food contact materials), data used as surrogate for pacifiers/teethers and infant toys
	Residual food content from packaging/processing "Antifoam" not TSCA-related, but conservatively included in the updated assessment[11]
	In the updated assessment, according to a study from Zhang, et al. (2012), D4 was detected in all samples of silicone nipples in concentrations ranging from 0.6 to 49 mg/kg (median 2.5 mg/kg; Table 5-16 and Table 5-18). A custom distribution was used to reflect the sampling results in the current exposure assessment and replace the estimate in the Canadian assessment which, as mentioned above, was a conservative overestimate. This value was used as a surrogate for those products applicable to EPA TSCA exposure assessments (pacifiers, infant toys).
OTC products - oral	The OTC products are likewise excluded because the OTC anti-gas products are considered a drug and fall under the purview of FDA
Cosmetic- oral	Oral exposure to consumer products was limited to ingestion of lipstick, which was incorporated in the overall oral exposure estimate in the general population model in the Canadian assessment. Because this is a use that is TSCA non-relevant, it was excluded from the updated assessment.
Indoor air (breathing zone air) - inhalation	In the updated assessment, breathing rates (Table 5-17) were updated with values from Table 6-4 (U.S.EPA 2011c) and were matched as closely as possible to the age ranges from the original assessment.
	In the updated assessment, concentrations of D4 in indoor air were taken from Tran and Kannan (2015) who reported on a survey of homes in Albany, New York. The new values used for the distribution (median = 0.116 µg D4/m^3 air, Table 5-15) were on the same order of magnitude as the original values.

[11] Silicones used in Food Contact Materials are generally regulated as indirect food additives by the U.S. FDA under C.F.R., Title 21 on Food and Drugs, parts 170 to 199 [18]. Silicones are covered in many sections of this regulation, e.g. under section numbers 178.3570 (lubricants with incidental food contact), 177.2600 (rubber articles intended for repeated use), 177.2465 (polymethylmethacrylate / poly-(trimethoxysilylpropyl)methacrylate copolymers), 175.300 (resins and polymer coatings), 175.320 (resins and polymer coatings for polyolefin films), 177.1200 (cellophane) and 175.105 (adhesives). A database providing yearly updates can be accessed and searched on the website of the FDA. In the production of silicones, prior sanctioned ingredients and substances generally recognized as safe (GRAS) are also legally allowed (Food Packaging Forum, 2015).

Outdoor air - inhalation	In the updated assessment, breathing rates (Table 5-17) were updated with values from Table 6-4 (U.S. EPA 2011c) and were matched as closely as possible to the age ranges from the original assessment.
	In the updated assessment, the concentrations of D4 found in outdoor air were taken from Yucuis, et al. (2013), which reported on urban air in Chicago, Illinois. Updated values used for the distribution (median = 0.054 µg D4/m^3, Table 5-15) were two orders of magnitude lower than what was used in the Canadian assessment. These data are used since they are specific to the U.S.

5.1.4.3 Monte Carlo Method

Distributions were developed for almost all the parameters used to estimate exposure. As noted above, some distribution data could not be located, and in these cases, the parameter value is held constant. Two hundred thousand iterations were run to provide average and percentile values for exposure by each identified route and to provide stability in the distributions at the 95th percentile. Equations to combine the parameters are shown in the table of inputs for each exposure route (Table 5-15 and Table 5-16).

The reported exposures may be considered estimated intakes (on a body weight basis) for one day. That is, a single iteration of the Monte Carlo analysis could be interpreted as though looking at a snapshot of the population on a single day. However, this analysis does not take into consideration the number of years over which a product may be used. Thus, the exposures are not lifetime average daily doses.

The estimates provided in the Updated Assessment can be considered conservative because they assume that for each scenario, 100% of the population are 'users'. This contrasts with the Canadian Assessment (SEHSC 2008b) that was carried out where only a fraction of the population was assumed to participate in each of the varying exposure scenarios. Because it is unlikely that everyone in the population is exposed to D4 through all routes assessed in the current analysis, the combined exposure estimates per route of exposure as well as total exposure can be considered conservative.

Similar to the Canadian Assessment results, dermal is the primary exposure pathway for adults. For children, ingestion is the primary pathway for 0-6 months and females 4-11 years; dermal is the primary pathway for children 6 months - 4 years and males 4-11 years. It should be noted

that these estimates are based on dermal contact with personal care products and cosmetics and these products are being used as a surrogate for household cleaners in the Updated Assessment.

The exposure estimates presented below are based on the average exposure scenarios, with the 90th percentile estimates provided in Table 5-13 and Table 5-14.

Aggregated dermal exposure from application of personal care products / cosmetics evaluated in the Canadian assessment (as surrogate for household cleaners) was included as a conservative estimate of dermal exposure and thus the total adult exposure likely overestimates actual exposure from EPA-regulated products. The adult dermal exposure estimates range from 4.01 x 10^{-3} to 9.90 x 10^{-3} mg/kg-bw/day for males 20-59 years and females 12-19 years, respectively.

Total adult inhalation values ranged from 5.53 x 10^{-6} to 1.03 x 10^{-5} mg/kg-bw/day in females 60+ and males 12-19 years old, respectively. Overall, inhalation values were approximately one order of magnitude lower than the Canadian Assessment. The updated outdoor air concentration value (0.054 µg D4/m^3 in the U.S. vs. 1 µg D4/m^3 in Nordic environments) likely contributed to this difference.

Total adult ingestion exposure in the general population ranged from 3.11 x 10^{-6} to 4.32 x 10^{-6} in males 20-59 years and females 12-19 years, respectively. In subsistence fisherman populations, the range was slightly higher, between 2.40 x 10^{-5} in males 60+ and 3.36 x 10^{-5} in females 12-19 years. Despite performing a ‘users only’ analysis, all ingestion exposure estimates were two orders of magnitude lower than the Canadian Assessment. In addition to lower totals for each stratum within ingestion in the update analysis, there were fewer categories considered; both factored into the lower overall ingestion exposure estimates.

Total adult exposure estimates ranged from 4.02 x 10^{-3} to 9.91 x 10^{-3} mg/kg-bw/day in males 20-59 and females 12-19 years old, respectively. In subsistence fishing populations, the total adult exposure ranged from 4.04 x 10^{-3} to 9.94 x 10^{-3} mg/kg-bw/day in males 20-59 and females 12-19 years old, respectively. These estimates were generally similar to the Canadian Assessment’s estimates.

For categories of exposure that included multiple strata (e.g., total ingestion for 6 months – 4 years), the highest stratum among the group was chosen as representative and included for reporting (e.g., total ingestion 7-11 months breastfed).

In children, total inhalation exposure estimates ranged from 1.23×10^{-5} to 2.12×10^{-5} mg/kg-bw/day in females 4-11 years and males 6 months-4 years, respectively. In comparison to the Canadian analysis, the inhalation values were approximately one order of magnitude lower than the original analysis.

Total child ingestion exposures ranged from 7.10×10^{5} to 3.85×10^{-3} mg/kg-bw/day in females 4-11 years and females 6 months - 4 years, respectively. In subsistence fishing populations, childhood ingestion exposure estimates ranged from 8.87×10^{-5} to 3.45×10^{-3} mg/kg-bw/day in females 4-11 years and breastfed infants 0-6 months, respectively. The ingestion exposure estimates in children were generally on the same order of magnitude as the Canadian Assessment.

Total childhood exposure estimates ranged from 8.63×10^{-5} to 1.39×10^{-2} mg/kg-bw/day in the general population females 4-11 years and females 6 months-4 years, respectively. In subsistence fishing populations, the exposure estimates ranged from 1.04×10^{-4} to 1.24×10^{-2} mg/kg-bw/day in females 4-11 years and both sexes 6 months-4 years, respectively. Except for the estimates in the 6 months-4 years age range, which were one order of magnitude higher than the Canadian Assessment, the updated estimates were one order of magnitude lower than the Canadian estimates.

The findings of the Updated Assessment indicated that all exposure estimates (with one exception, noted above) were either lower or of the same order of magnitude as the Canadian Assessment. Therefore, the Canadian Assessment and by extension the Gentry et al. (2017) exposure assessment can be used as a conservative approach to the evaluation of D4 consumer and general population exposures for this Risk Evaluation. Additional conservatism results from the fact that the Canadian Assessment, and therefore the Gentry et al. (2017) assessment, included non TSCA-relevant exposures.

5.1.4.4 Consumer and General Population Exposure Estimates Selected for Evaluation in the Risk Characterization

For consumer exposure (summarized in Table 5-10), the inhalation and dermal internal dose levels presented in Table 5-8 are included in the risk characterization of D4. Gentry et al. (2017) concluded oral exposures to consumer products (Tables 5-9 and 5-10) were largely incidental and not a major exposure pathway of concern, and therefore were not carried forward to risk characterization. For general population exposure (summarized in Table 5-11), indoor and outdoor air internal doses presented in Table 5-12 are selected for evaluation in the current risk characterization.

Dermal exposure to the general population was not considered a pathway of concern in Gentry et al. (2017). Oral exposures to the general population or to subsistence fisherman were not carried further in the risk evaluation because the exposure potential was determined by Gentry et al. (2017) to be two orders of magnitude less than the exposure representing the greatest exposure to D4 through consumer use (e.g. body lotion for adults).

5.1.4.5 Uncertainty in the Human Health Exposure Assessment

The US EPA Exposure Factors Handbook (EFH) (U.S. EPA 2008, 2011c) identifies key types of uncertainty that contribute to overall uncertainty in risk assessment. All the types of uncertainty noted below contribute or may contribute to the overall uncertainty in the estimates of exposure to D4 presented here.

Three types of uncertainty and associated sources and examples		
Type of uncertainty	*Sources*	*Examples*
Scenario uncertainty	Descriptive error	Incorrect or insufficient information
	Aggregation errors	Spatial or temporal approximations
	Judgment errors	Selection of incorrect model
	Incomplete analysis	Overlooking an important pathway
Parameter uncertainty	Measurement errors	Imprecise or biased measurements
	Sampling errors	Small or unrepresentative samples
	Surrogate data	Structurally-related chemicals
Model uncertainty	Relationship error	Incorrect inferences on the basis for correlations
	Modeling error	Excluding relevant variables

Source: U.S. EPA 2008, 2011c

An example of scenario uncertainty may be found in the attempt to quantify the D4 exposure via food consumption. No experimental measurements of D4 in foodstuffs, except for certain fish and marine foods were identified. Therefore, PECs of D4 in certain media were used to represent the potential range of exposures via this route. However, without some experimental identification that these are the appropriate food types to include in a food analysis, and without experimental determination of D4 concentrations, there is uncertainty about the contribution of this pathway to overall exposure.

The major source of uncertainty in this analysis is expected to be parameter uncertainty; in several cases, there is either very limited, or no data to quantify the amount of D4 available for human exposure via a particular pathway.

Sources of parameter uncertainty include both measurement error and sampling error, as well as use of surrogate data. For example, surface water data collected from the mixing zone was used as a surrogate for drinking water. In another example, for soil concentrations, only 11 samples were taken with only three detectable concentrations. Relying on so few samples to represent all soil concentrations introduces uncertainty into the model. An additional example of parameter uncertainties includes the limited D4 concentration data for many products and that data based on reported concentrations could be in a formulation that is conservative, but may not represent actual practice and the range of D4 concentrations.

There are also uncertainties in the exposure estimates that have not been quantified, and these may outweigh the differences in D4 exposure between general and subsistence populations.

An important source of uncertainty in the estimates of exposure for children come from the use patterns of juvenile products made from silicone elastomers. For example, it is not known with certainty the extent of the population that use silicone-based pacifiers, teethers or infant toys. In these cases, professional judgment was used to develop placeholder distributions in lieu of data. Furthermore, ingestion exposure was not differentiated for boys and girls under 4 years of age because there was little information on which to base such a separate estimate. The children’s population groups were separated by lactation status, since this was assumed to impact the

ingestion of D4 from water, milk, human milk, and certain elastomeric products, such as baby bottle nipples. These are only a few of the sources of uncertainty in the assessment.

Approaches to quantitative analysis of uncertainty		
Approach	**Description**	**Example**
Sensitivity analysis	Changing one input variability at a time while leaving others constant, to example effect on output	Fix each input at lower (then upper) bound while holding others at nominal values (e.g., medians)
Analytical uncertainty propagation	Examining how uncertainty in individual parameters affects the overall uncertainty of the exposure assessment	Analytically or numerically obtain a partial derivative of the exposure equation with respect to each input parameter
Probabilistic uncertainty analysis	Varying each of the input variability's over various values of their respective probability distributions	Assign probability density function to each parameter: randomly sample values from each distribution and insert them in the exposure equation (Monte Carlo)
Classical statistical methods	Estimating the population exposure distribution directly, based on measure values from a representative sample	Compute confidence intervals for various percentiles of the exposure distribution

Source: U.S. EPA 2008, 2011c

Table 5-1. Comparison of silicone worker inhalation exposure parameters

Worker	Parameter					
	Air Concentration[a] (ppm/µg/m³)	**Daily Exposure[d] (hours/day)**	**Exposure Frequency[d] (days/week)**	**Work Year[d] (weeks/year)**	**Inhalation Rate[e] (m³/h)**	**Body Weight[f] (kg)**
Silicone Worker – D4 production facility (Maxim 1988, as cited in Gentry et al. 2017)	0.1908/2310 (0.0950)[b]	8.75[d]	5	50	1.6 (M)	86.9 (M)
					1.4 (F)	73.4 (W)
Manufacture / Processing (SEHSC 2019)	1.2/14,558[c]	8	5	50	1.6 (M)	86.9 (M)
					1.4 (F)	73.4 (W)

[a]Values are reported as arithmetic mean (geometric mean). The arithmetic mean was used in the assessment. Results from Maxim (1998) unless otherwise specified.

[b]Arithmetic and geometric mean concentrations from air concentration monitoring in D4 production facility, as summarized in Gentry et al. (2017)

[c]Results from SEHSC (2019) worker exposure personal inhalation monitoring

[d]Defaults based upon professional judgment.

[e]Inhalation rates as reported in USEPA (2011c).

[f]Body weights based upon NHANES (CDC 2007–2010) data.

Table 5-2. Summary of worker inhalation exposure parameters (from Gentry et al. 2017)

Worker	Parameter					
	Air Concentration[a] (ppm/µg/m³)	**Daily Exposure[e] (hours/day)**	**Exposure Frequency[e] (days/week)**	**Work Year[e] (weeks/year)**	**Inhalation Rate[f] (m³/h)**	**Body Weight[g] (kg)**
Antiperspirant (formulation)	0.33/4000 (0.15)	8	5	50	1.6 (M)	86.9 (M)
					1.4 (F)	73.4 (W)
Skin Care (formulation)	2.44/29,600 (1.76)	8	5	50	1.6 (M)	86.9 (M)
					1.4 (F)	73.4 (W)
Hair Care (formulation)	0.012/150 (0.007)	8	5	50	1.6 (M)	86.9 (M)
					1.4 (F)	73.4 (W)
Silicone workers	0.1908/2310 (0.0950)[b]	8.75c	5	50	1.6 (M)	86.9 (M)
					1.4 (F)	73.4 (W)
Barbers and Beauticians	0.085[a]/1000	5.6 or 7[d]	4 or 5	50	1.6 (M)	86.9 (M)
					1.4 (F)	73.4 (W)
Office workers	0.000383/5	8	5	50	1.6 (M)	86.9 (M)
	0.000781/10.2				1.4 (F)	73.4 (W)

[a]Values are reported as arithmetic mean (geometric mean). The arithmetic mean was used in the assessment. Results from Maxim (1998) unless otherwise specified.

[b]Arithmetic and geometric mean concentrations from air concentration monitoring in D4 production facility, as summarized in Gentry et al. (2017)

[c]Based upon results for silicone workers as reported in (Maxim 1998).

[d]Based upon The U.S. Department of Labor Bureau of Labor Statistics (2012).

[e]Defaults based upon professional judgment.

[f]Inhalation rates as reported in USEPA (2011c).

[g]Body weights based upon NHANES (CDC 2007–2010) data.

Table 5-3. Occupational inhalation exposure expressed as internal dose (Area Under the Curve, AUC) (from Gentry et al. 2017)

Worker	AUC (mg-hr/L blood/day)	
	Men	**Women**
Inhalation		
Antiperspirant (formulation)	1.95×10^{-2}	1.07×10^{-2}
Skin Care (formulation)	1.44×10^{-1}	7.88×10^{-2}
Hair Care (formulation)	7.09×10^{-4}	3.88×10^{-4}
Silicone Workers	1.23×10^{-2}	6.74×10^{-3}
Barbers and Beauticians		
5 days	3.63×10^{-3}	2.03×10^{-3}
4 days	3.60×10^{-3}	2.01×10^{-3}
Office Worker		
5 $\mu g/m^3$ (0.000383 ppm)	2.26×10^{-5}	1.24×10^{-5}
10.2 $\mu g/m^3$ (0.000781 ppm)	4.61×10^{-4}	2.50×10^{-5}
Dermal		
Barbers and Beauticians		
5 days	8.98×10^{-4}	2.16×10^{-3}
4 days	1.14×10^{-3}	2.73×10^{-3}

Table 5-4. Summary of worker exposure assessment

Route of exposure	Source of exposure INCLUDED in this assessment	Exposure Value	Internal dose value used*	
Oral	Not applicable			
Dermal	Barbers and beauticians (not TSCA relevant)	14.1 mg of D4 exposure per application	5 days	8.98×10^{-4} (men) 2.16×10^{-3} (women)
			4 days	1.14×10^{-3} (men) 2.73×10^{-3} (women)
Inhalation	Silicone worker exposure (based on formulation of skin care products used as a conservative estimate for all D4 workers)	2.4 ppm (29,600 µg/m^3)	**0.144 (men)** **0.0778 (women)**	
	Barbers and beauticians (not TSCA relevant)	0.085 ppm (1000 µg/m^3)	5 days	3.60×10^{-3} (men) 2.03×10^{-3} (women)
			4 days	3.63×10^{-3} (men) 2.01×10^{-3} (women)
	Office workers (not TSCA relevant)	0.000383 ppm (5 µg/m^3)	2.26×10^{-5} (men) 1.24×10^{-5} (women)	
		0.000781 ppm (10.2 µg/m^3)	4.61×10^{-4} (men) 2.50×10^{-5} (women)	

Values in bold serve as conservative values for all TSCA relevant worker exposures. See Table 5-3 for all internal dose values.

Table 5-5. Application parameter values for consumer use (Gentry et al. 2017)

Product	Application rate (gms/day)	Application Frequency (application/	Midpoint D4 (%)[b]
Antiperspirant/ Deodorant gel or roll-on Antiperspirant/	1.22 (male)[c]	1.3	9.5
	0.898 (female)[c]		
Antiperspirant/ Deodorant stick or solid	0.79 (male) [f]	1.3	9.5
	0.61 (female)[f]		
Antiperspirant/ Deodorant aerosol	3.478 [c]	1	9.5
Shampoo	6[c]	1	0.002
Conditioner (Leave-in)	13.77[e]	1	1.0
Conditioner (Rinse- out)	13.77[e]	1	1.0
Hair care-hair spray Aerosol	3.57[f]	1	41.2[i]
Pump	5.18[f]	1	41.2[i]
Cosmetic foundation	0.33[g]	1	19
Cosmetic night cream/ under eye cream	0.06[a]	1	9.5
Cosmetic mascara	0.11[a]	2	6.5
Cosmetic lipstick	0.025[c]	3	14
Skin care-after-shave gel	0.95[a]	1	11.5
Skin care-lotion (hand/body)	8.69[c]	1	5.52
Skin care-Moisturizer	0.91[c]	1	2.0
Skin care-nail care	0.25[a]	1	10
Skin care-sunscreen	6.1[a]	1	0.31
Soothing Vapor	5[d]	2	0.45

Note: all citations below as found in Gentry et al. 2017
[a]Maxim (1998).
[b]Midpoints calculated from Johnson et al. (2011).
[c]Hall et al. (2007).
[d]Meeks (2005).
[e]Loretz et al. (2008).
[f]Loretz et al. (2006).
[g]Hall et al. (2011).
[h]Personal judgment.
[i]Wang et al. (2009).

Table 5-6. Surface area for dermal evaluation of consumer exposure to antiperspirant/deodorant, hair care, and skin care products (Gentry et al. 2017)

Product Type	Surface Area (cm^2)		Area Description	Basis[a]
	Male	Female		
Antiperspirant/Deodorant – gel/roll-on, stick/solid, and aerosol	271	129	Both axillae	Cowan-Ellsberry et al., 2008
Hair care – hair spray (aerosol and pump)	680	570	½ head (hair sprays)	SCCS, 2012; USEPA, 2011
	1215	1015	½ area head + ½ hands (conditioners)	
	1750	1460	½ area head + total area of hands (shampoo)	
Cosmetics – foundation	NA	570	½ head	SCCS, 2012; USEPA, 2011
Skin Care – moisturizer				
Cosmetics – night cream/under-eye cream	NA	24	Assume is same as area for eye shadow	SCCS, 2012
Cosmetics – Mascara	NA	1.6		SCCS, 2012
Skin Care – after shave gel	340	NA	¼ head	USEPA, 2011
	535		½ hands	
Skin Care – lotion (hand/body), sunscreen	20,670	17,000	Body — head	USEPA, 2011
Skin Care – nail care	NA	11	Estimate of skin around nail	SCCS, 2003
Soothing Vapor	4175	3270	½ of Trunk	USEPA, 2011

[a] All citations from Gentry et al. 2017.

Table 5-7. Consumer inhalation exposure used by Gentry et al. (2017)

Parameter	Men	Women
Air Concentration (AC)		
AP/D Solid	0.024 ppm (290 µg/m^3)	0.024 ppm (290 µg/m^3)
AP/D Roll-on	1.82 ppm (22,000 µg/m^3)	1.82 ppm (22,000 µg/m^3)
AP/D Aerosol	0.94 ppm (11,400 µg/m^3)	0.94 ppm (0.0114 µg/m^3)
HC/SC Products	0.338 ppm (4000 µg/m^3)	0.338 ppm (4000 µg/m^3)
Exposure Duration (ED)	5 min/day	10 min/day
Inhalation Rate (INH)	0.8 m^3/hour	0.7 m^3/hour
Body Weight (BW)	86.9 kg	73.4 kg
[a]Median time spent in bathroom following a shower or bath.		
[b]Due to the limitations of the PBPK model, the inhalation times were run for 7 days per week for an exposure duration equal to ED * AF/7 min per day.		

Table 5-8. Internal dose levels expressed as Area under the Curve (AUC) exposure from selected consumer products (Gentry et al. 2017)

Product	AUC (mg-hr/L blood/day)	
	Men	**Women**
Dermal		
Solid Deodorant	4.15×10^{-4}	3.97×10^{-4}
Roll-on Deodorant	4.82×10^{-6}	2.58×10^{-6}
Aerosol Deodorant	9.17×10^{-4}	1.19×10^{-3}
Shampoo	6.02×10^{-9}	1.51×10^{-8}
Conditioner (Rinse-out)	7.14×10^{-6}	1.74×10^{-5}
Conditioner (Leave-in)	3.57×10^{-5}	8.71×10^{-5}
Hair spray (aerosol)	9.01×10^{-9}	2.24×10^{-8}
Hair spray (pump)	1.31×10^{-8}	3.26×10^{-8}
Moisturizer	9.53×10^{-5}	2.32×10^{-4}
Foundation	N/A	5.41×10^{-4}
Night cream/Under eye cream	N/A	6.14×10^{-4}
Lipstick (6 days)	N/A	7.56×10^{-5}
Lipstick (5 days)	N/A	3.12×10^{-5}
Mascara	N/A	1.44×10^{-4}
Hand/body lotion	2.49×10^{-3}	3.14×10^{-3}
Sunscreen	1.31×10^{-7}	3.15×10^{-7}
Nail care	N/A	8.93×10^{-7}
After-shave gel	4.05×10^{-4}	N/A
Soothing vapor	7.54×10^{-9}	1.77×10^{-8}
Inhalation		
Solid Deodorant	2.68×10^{-5}	3.04×10^{-5}
Roll-on Deodorant	2.04×10^{-3}	2.31×10^{-3}
Aerosol Deodorant	1.05×10^{-3}	1.16×10^{-3}
Hair spray (aerosol)	4.16×10^{-4}	4.71×10^{-4}
Hair spray (pump)	4.16×10^{-4}	4.71×10^{-4}
Moisturizer	4.16×10^{-4}	4.71×10^{-4}
Foundation	N/A	4.71×10^{-4}
Hand/body lotion	4.16×10^{-4}	4.71×10^{-4}
Sunscreen	4.16×10^{-4}	4.71×10^{-4}
Nail care	N/A	4.71×10^{-4}
After-shave gel	4.16×10^{-4}	N/A
Soothing vapor	2.74×10^{-6}	1.55×10^{-6}

Table 5-9. Oral exposure parameters for Monte Carlo analysis (Gentry et al. 2017)

Exposure		Parameter	Value for Both Genders	Units	Distribution	Min	Median / Most Likely	Max	Mean/Std[a]	Source (as cited in Gentry et al. 2017)
Adult	Lipstick (only oral consumer exposure; therefore, added to general population oral exposure)	Amount of D_4 in product	0.14	fraction	Constant					Johnson et al. 2011
		Use frequency	1	times/wk	Custom	0	1.7	7		Loretz et al. 2005
		Amount per use	0.024	g/application	Lognormal	0		0.214	0.14/3.45 (G)	Loretz et al. 2005
		Body weight	Varies by age	kg	See Body Weights Table S7 for specific body weights by age					CDC (2007-2010)
		Bioavailability	0.52	Fraction	Normal	0.37		0.67	0.52/0.05	Dow Corning Corporation 1998
	OTC Antigas	Amount AA AG per use	0.01	g	Lognormal	0		0.214	0.01/3.29 (G)	
		Frequency of use	4	times/day	Triangular	1	4	12		Dow Corning Corporation 1999
		Conc. of D_4 in AA AG	3	µg/g product	Triangular	1	3	4		Dow Corning Corporation 1999
		Bioavailability	0.12	Fraction		0.08		0.15	0.12/0.01	Dow Corning Corporation 1998
		Body weight	Varies by age and gender	kg	See Body Weights Table S7 for specific body weights by age and gender					CDC (2007-2010)
	Food / Milk	Amount Consumed	Varies by age and gender	g/kg Bw/day	Data obtained from CSFIII (USDA 1998) and custom distributions for age, gender and food product were derived.					
		Conc of D_4	Values in mg/kg (Empirical distributions)		**Fish**	**Root crops**	**Plant leaves**	**Meat**	**Milk**	Brooke et al. 2009; Environmental Control Center Co. Ltd. 2011; Norden 2005; NILU 2007
					0.0013 to 40	1.2×10^{-4} to 0.055	5.6×10^{-7} to 0.019	1.3×10^{-4} to 0.45	4.2×10^{-5} to 0.14	

Table 5-9. Oral exposure parameters for Monte Carlo analysis (Gentry et al. 2017)

Exposure		Parameter	Value for Both Genders	Units	Distribution	Min	Median / Most Likely	Max	Mean/Std[a]	Source (as cited in Gentry et al. 2017)
Adult		Bioavailability	0.52	Fraction	Normal	0.37		0.66	0.52/0.0497	Dow Corning Corporation 1998
	Subsistence Fisherman Fish and Shellfish	Amount Consumed	59	g/day	Truncated Normal	0		170	59/67.5[b]	USEPA 2011
		Conc of D_4	20	mg/kg		0.0013	40			Brooke et al. 2009; Environmental Control Center Co. Ltd. 2011; Norden 2005; NILU 2007
		Conversion from g to kg	1×10^{-3}		Constant					
		Bioavailability	0.52	Fraction	Normal	0.37		0.66	0.52/0.0497	Dow Corning Corporation 1998
	Water	Amount Consumed	Varies by age and gender from 0 to 4 L/day	L/day	Includes tap water and foods and beverages derived from tap water. Source: Canadian Ministry of National Health and Welfare 1981. Tap water consumption in Canada. Document number 82-EHD-80. Public Affairs Directorate, Department of National Health and Welfare, Ottawa, Canada.					
		Conc of D_4	2×10^{-4}	mg/L		3×10^{-7}		4×10^{-4}		Brooke et al. 2009
		Bioavailability	0.52	Fraction	Normal	0.37		0.66	0.52/0.0497	Dow Corning Corporation 1998
Adult	Antifoam	Total Food Consumed	Varies by age and gender	g/kg Bw/day	Data obtained from CSFIII (USDA 1998) and custom distributions for age, gender were derived for total intake in a day. 50% of total intake was assumed to contain some antifoam.					
		Conc of Antifoam in Food	5	mg	Triangular	0	5	10		Dow Corning Corporation 2004a, 2007; European Commission 2011; Dow Corning Corporation 1999; USFDA 2012
		Conc of D_4 in antifoam	0.49	Fraction	Constant					Dow Corning Corporation 1999

Table 5-9. Oral exposure parameters for Monte Carlo analysis (Gentry et al. 2017)

Exposure		Parameter	Value for Both Genders	Units	Distribution	Min	Median / Most Likely	Max	Mean/Std[a]	Source (as cited in Gentry et al. 2017)
		Bioavailability	0.12	Fraction	Normal	0.08		0.15	0.12/0.01	Dow Corning Corporation 1998
	Soil	Soil Consumed	50	mg	Constant					USEPA 2011
		Conc of D_4 in soil	38	µg/kg of dirt	Uniform	3		74		Norden 2005
		Conversion from mg to kg and µg to mg	1×10^{-6}		Constant					
		Bioavailability	0.52	Fraction	Normal	0.37		0.67	0.52/0.05	Dow Corning Corporation 1998
Children	OTC Antigas	Amount AA AG per use	0.01	g	Lognormal				0.01/3.29 (G)	Meeks 2005
		Frequency of use	4	times/day	Triangular	1	4	12		Dow Corning Corporation 1999
		Conc. of D_4 in AA AG (children)	169	µg/g product	Triangular	163	169	181		Dow Corning Corporation 1999
Children		Conc. of D_4 in AA AG (infant)	21.5	µg/g product	Triangular	21	21.5	39		Dow Corning Corporation 1999
		Bioavailability	0.52	Fraction	Normal	0.37		0.67	0.52/0.05	Dow Corning Corporation 1998
		Body weight	Varies by age and gender	kg	See Body Weights Table S7 for specific body weights by age and gender					CDC (2007-2010)
	Baby Bottle Nipples /Pacifiers /Sipper Tubes /Straws	Concentration of D_4	2.4	mg D_4 /kg product	Triangular	0.6	2.4	49		Zhang et al. 2012
		Product weight Baby Bottle	10	g	Triangular	9.5	10	10.5		Dow Corning Corporation 2004b, 2007

Table 5-9. Oral exposure parameters for Monte Carlo analysis (Gentry et al. 2017)

Exposure		Parameter	Value for Both Genders	Units	Distribution	Min	Median / Most Likely	Max	Mean/Std[a]	Source (as cited in Gentry et al. 2017)
Children		Nipple/Pacifiers								
		Product weight Sipper Tubes	5	g	Triangular	4.75	5	5.25		Dow Corning Corporation 2004b, 2007
		Product weight Straws	2	g	Triangular	1.9	2	2.1		Dow Corning Corporation 2004b, 2007
		Migration Factor	0.0045		Constant					Zhang et al. 2012
		Bioavailability	0.52	Fraction	Normal	0.37		0.66	0.52/0.0497	Dow Corning Corporation 1998
		Body weight	Varies by age and gender	kg	See Body Weights Table S7 for specific body weights by age and gender					CDC (2007-2010)
	Food / Milk	Amount Consumed	Varies by age and gender	g/kg Bw/day	Data obtained from CSFIII (USDA 1998) and custom distributions for age, gender and food product were derived.					
		Conc of D_4	Values in mg/kg (Empirical distributions)		**Fish**	**Root crops**	**Plant leaves**	**Meat**	**Milk**	Brooke et al. 2009; Environmental Control Center Co. Ltd. 2011; Norden 2005; NILU 2007
					0.0013 to 40	1.2×10^{-4} to 0.055	5.6×10^{-7} to 0.019	1.3×10^{-4} to 0.45	4.2×10^{-5} to 0.14	
		Bioavailability	0.52	Fraction	Normal	0.37		0.66	0.52/0.0497	Dow Corning Corporation 1998
	Subsistence Fisherman Fish and Shellfish	Amount Consumed	25	g/day	Truncated Normal	0		73	25/29.2[b]	Child Specific EFH USEPA (2006) Table 3-57 Native American (consumers only) from CRITFC 1994

Table 5-9. Oral exposure parameters for Monte Carlo analysis (Gentry et al. 2017)

Exposure		Parameter	Value for Both Genders	Units	Distribution	Min	Median / Most Likely	Max	Mean/Std[a]	Source (as cited in Gentry et al. 2017)
		Conc of D_4	20	mg/kg		0.0013	40			Brooke et al. 2009; Environmental Control Center Co. Ltd. 2011; Norden 2005; NILU 2007
		Conversion from g to kg	1×10^{-3}		Constant					
		Bioavailability	0.52	Fraction	Normal	0.37		0.66	0.52/0.0497	Dow Corning Corporation 1998
	Water	Amount Consumed	Varies 0 to 2.36 L/day	L/day	Includes tap water and foods and beverages derived from tap water. Source: Canadian Ministry of National Health and Welfare 1981. Tap water consumption in Canada. Document number 82-EHD-80. Public Affairs Directorate, Department of National Health and Welfare, Ottawa, Canada.					
		Conc of D_4	2×10^{-4}	mg/L		3×10^{-7}		4×10^{-4}		Brooke et al. 2009
		Bioavailability	0.52	Fraction	Normal	0.37		0.66	0.52/0.0497	Dow Corning Corporation 1998
Children	**Breast Milk**	Amount Consumed	Varies by age	mL/day	Based on the mean and max values from Table 15-1 in the Child Specific Exposures Factors Handbook (USEPA 2006), Normal distributions were derived using the reported mean and 1/2 the distance from the mean to the Upper percentile as the standard deviation.					
		Conc of D_4	2	µg/L		2	2	10		Kaj et al. 2005
		Conversion from mL to L and µg to mg	1×10^{-6}		Constant					
		Bioavailability	0.52	Fraction	Normal	0.37		0.66	0.52/ 0.0497	Dow Corning Corporation 1998
	Antifoam	Total Food Consumed	Varies by age and gender	g/kg Bw/day	Data obtained from CSFIII (USDA 1998) and custom distributions for age, gender were derived for total intake in a day. 50% of total intake was assumed to contain some antifoam.					
		Conc of Antifoam in Food	5	mg	Triangular	0	5	10		Dow Corning Corporation 2004b, 2007; European Commission 2011; Dow

Table 5-9. Oral exposure parameters for Monte Carlo analysis (Gentry et al. 2017)

Exposure		Parameter	Value for Both Genders	Units	Distribution	Min	Median / Most Likely	Max	Mean/Std[a]	Source (as cited in Gentry et al. 2017)
										Corning Corporation 1999; USFDA 2012
		Conc of D_4 in antifoam	0.49	Fraction	Constant					Dow Corning Corporation 1999
		Bioavailability	0.12	Fraction	Normal	0.08		0.15	0.12/0.01	Dow Corning Corporation 1998
Children	Soil	Soil Consumed	100	mg/day	Truncated Normal	0		400	100/182[b]	USEPA 2006
		Conc of D_4 in soil	38	µg/kg of dirt	Uniform	3		74		Norden 2005
		Conversion from mg to kg and µg to mg	1×10^{-6}		Constant					
		Bioavailability	0.52	Fraction	Normal	0.37		0.67	0.52/0.05	Dow Corning Corporation 1998

[a] Geometric Means and Standard Deviations are indicated with a G

[b] Standard deviation estimated. Truncated Normal distribution defined with minimum, mean and 95th%tile.

Table 5-10. 95th Percentile on exposure in mg/kg BW/day from Monte Carlo analysis*																
Exposure Source	**0 to 6 months**			**7-11 months**	**< 1 to 4 years**			**2 to 4 years**	**4 to 11 years**		**12 to 19 years**		**20 to 59 years**		**60 + years**	
	Both	**Female**	**Male**	**Both**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
AP Spray											7.6E-3	6.9E-3	6.2E-3	5.2E-3	6.3E-3	5.3E-3
After Shave												1.7E-3		1.3E-3		1.3E-3
Antifoam								2.7E-3	1.7E-3	1.8E-3	1.2E-3	1.6E-3	1.3E-3	1.4E-3	1.1E-3	1.1E-3
Baby Bottle Nipple	1.5E-4			1.0E-4	8.3E-5											
Body Lotion									1.5E-2	1.5E-2	1.3E-2	1.2E-2	1.0E-2	8.8E-3	1.1E-2	9.0E-3
Conditioner Leave in									2.7E-6	0.0E+00	1.7E-6	0.0E+00	1.4E-6	0.0E+00	1.4E-6	0.0E+00
Conditioner Rinse off									2.3E-7	0.0E+00	8.2E-8	0.0E+00	6.6E-8	0.0E+00	6.8E-8	0.0E+00
Dermal Soothing Vapor						6.6E-6	6.1E-6		2.9E-6	2.9E-6	1.7E-6	1.5E-6	1.4E-6	1.1E-6	1.4E-6	1.2E-6
Diaper Cream		3.5E-4	3.3E-4			1.8E-4	1.6E-4									
Fish	8.9E-7			8.2E-5				1.3E-4	9.8E-5	1.1E-4	5.5E-5	7.5E-5	5.9E-5	6.0E-5	6.7E-5	5.8E-5
Foundation											3.7E-3		3.0E-3		3.1E-3	
Greens	5.8E-8			3.8E-8	8.6E-8			7.1E-8	7.5E-8	6.2E-8	7.8E-8	8.1E-8	1.2E-7	1.1E-7	1.6E-6	1.3E-7
Hair Spray											5.2E-3	2.6E-3	4.2E-3	2.0E-3	4.3E-3	2.1E-3
Breast Milk	1.2E-3			7.9E-4	4.3E-4											
Indoor Air		1.3E-3	1.2E-3			1.2E-3	1.2E-3		7.3E-4	8.0E-4	3.4E-4	4.2E-4	2.5E-4	2.9E-4	2.3E-4	2.6E-4
Lipstick Ingestion											9.4E-5		7.6E-5		7.9E-5	
Mascara											1.0E-4		8.5E-5		8.7E-5	
Meat	1.2E-4			1.7E-4	3.0E-4			4.2E-4	2.9E-4	3.2E-4	6.5E-5	9.1E-5	5.6E-5	7.9E-5	4.9E-5	5.7E-5
Meat Not Breastfed	1.3E-4			2.7E-4												
Milk	1.1E-4			1.3E-4	9.6E-4			7.4E-4	3.8E-4	4.4E-4	1.1E-4	1.9E-4	5.5E-5	5.8E-5	6.4E-5	7.4E-5
Moisturizer											1.1E-3		9.1E-4		9.4E-4	
Nail Care											9.5E-4		7.7E-4		7.9E-4	
Over the Counter Anti-Gas		8.6E-5	4.4E-5			2.7E-4	2.5E-4		1.1E-4	1.1E-4	2.2E-6	2.0E-6	1.8E-6	1.5E-6	1.8E-6	1.6E-6

Table 5-10. 95th Percentile on exposure in mg/kg BW/day from Monte Carlo analysis*																
Exposure Source	**0 to 6 months**			**7-11 months**	**< 1 to 4 years**			**2 to 4 years**	**4 to 11 years**		**12 to 19 years**		**20 to 59 years**		**60 + years**	
	Both	**Female**	**Male**	**Both**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
Outdoor Air		2.8E-3	2.6E-3			2.7E-3	2.5E-3		1.6E-3	1.7E-3	7.4E-4	9.2E-4	5.5E-4	6.5E-4	5.1E-4	5.7E-4
Pacifier	1.5E-4			1.0E-4	8.3E-5			6.1E-5								
Roll on-AP											2.1E-3	2.9E-3	1.7E-3	2.1E-3	1.7E-3	2.2E-3
Root Crops	1.2E-5			1.5E-5	1.1E-5			9.2E-6	6.5E-6	7.0E-6	4.1E-6	5.0E-6	3.8E-6	4.5E-6	4.0E-6	4.3E-6
Shampoo		9.7E-6	1.6E-5			4.8E-6	7.7E-6		7.7E-9	1.2E-8	5.3E-9	3.0E-9	4.2E-9	2.3E-9	4.3E-9	2.4E-9
Sipper Tube	7.7E-5			5.0E-5	4.1E-5			3.0E-5	1.7E-5	1.7E-5						
Soil	3.0E-4			2.0E-4	1.6E-4			1.2E-4	6.6E-5	6.6E-5	7.1E-6	6.6E-6	5.8E-6	4.8E-6	5.8E-6	4.9E-6
Solid AP											3.0E-3	3.0E-3	2.4E-3	2.2E-3	2.5E-3	2.3E-3
Soothing Vapor Inhalation						2.0E-4	1.8E-4		1.2E-4	1.3E-4	1.5E-4	1.8E-4	1.1E-4	1.3E-4	1.0E-4	1.1E-4
Spray Detangler		1.2E-4	1.9E-4			5.7E-5	9.2E-5		2.4E-5	4.3E-5						
Straw	2.9E-5			1.9E-5	1.6E-5			1.2E-5	6.6E-6	6.7E-6						
Subsistence Fish Eating								1.8E-4	9.6E-5	9.9E-5	1.1E-4	1.0E-4	9.3E-5	8.0E-5	9.5E-5	8.2E-5
Sun Screen		7.0E-5	6.5E-5			8.5E-5	7.9E-5		7.0E-5	7.1E-5	6.1E-6	5.5E-6	4.9E-6	4.2E-6	5.1E-6	4.3E-6
Under Eye Cream													1.2E-4		1.2E-4	
Water	3.2E-7			2.1E-7	1.7E-7			1.3E-7	7.1E-8	7.1E-8		4.9E-8	4.9E-8	4.1E-8	4.9E-8	4.2E-8

* Consumer exposures listed in Table 5-8 amd general population exposures listed in Table 5-9.

Table 5-11. Summary of general population inhalation exposures used by Gentry et al. (2017)

Parameter	Value
Air Concentration	
Indoor	0.000766 ppm (10 µg/m^3)
Outdoor	0.0000153 ppm (0.2 µg/m^3)
Exposure Duration – Indoor and Outdoor[a]	24 h/day
Frequency	7 days/week; 52 weeks/year
Inhalation Rates	
Males	0.8 m^3/hour
Females	0.7 m^3/hour
Body Weights	
Males	86.9 kg
Females	73.4 kg

[a]Since the PBPK model is set up for accounting for varying inhalation exposure during the day, 24 h exposure to either indoor and outdoor air was assumed.

Table 5-12. Internal dose levels expressed as Area under the Curve (AUC) exposure from inhalation for the general population (residential 20–59 yr olds; Gentry et al., 2017)

Location	**AUC (mg-hr/L blood/day)**	
	Men	**Women**
Indoor (10 µg/m^3)	1.9×10^{-4}	1.08×10^{-4}
Outdoor (0.2 µg/m3)	3.8×10^{-6}	2.15×10^{-6}

Table 5-13. Summary of exposure estimates for adults, mg/kg-bw/day[a]

Adults	12-19 years		20-59 years		60 + years	
Average (mg/kg-bw/d)	**M**	**F**	**M**	**F**	**M**	**F**
Dermal[b]	5.19E-03	9.90E-03	4.01E-03	8.32E-03	4.12E-03	8.56E-03
Inhalation	9.00E-05	7.36E-05	6.51E-05	5.61E-05	5.68E-05	5.21E-05
Updated inhalation[c]	1.03E-05	8.77E-06	7.94E-06	7.35E-06	6.07E-06	5.53E-06
Ingestion, general population	2.15E-04	2.20E-04	2.36E-04	2.81E-04	2.60E-04	3.25E-04
Updated ingestion, general population	4.03E-06	4.32E-06	3.11E-06	3.66E-06	3.21E-06	3.86E-06
Ingestion, subsistence eaters	1.10E-03	1.22E-03	8.43E-04	9.97E-04	8.63E-04	1.03E-03
Updated ingestion, subsistence eaters	3.03E-05	3.36E-05	2.65E-05	2.76E-05	2.40E-05	2.87E-05
Total exposure, general population	5.50E-03	1.02E-02	4.31E-03	8.66E-03	4.44E-03	8.94E-03
Updated total exposure, general	5.20E-03	9.91E-03	4.02E-03	8.33E-03	4.13E-03	8.57E-03
Total exposure, subsistence population	6.43E-03	1.13E-02	4.95E-03	9.46E-03	5.08E-03	9.74E-03
Updated total exposure, subsistence	5.23E-03	9.94E-03	4.04E-03	8.35E-03	4.15E-03	8.59E-03

Adults	12-19 years		20-59 years		60 + years	
90th percentile (mg/kg-bw/d)	**M**	**F**	**M**	**F**	**M**	**F**
Dermal[b]	1.53E-02	2.36E-02	1.18E-02	1.95E-02	1.21E-02	2.01E-02
Inhalation	1.48E-04	1.21E-04	1.06E-04	9.14E-05	9.31E-05	8.51E-05
Updated inhalation[c]	1.73E-05	1.47E-05	1.32E-05	1.23E-05	1.02E-05	9.32E-06
Ingestion, general population	1.38E-04	2.39E-04	1.14E-04	2.24E-04	1.17E-04	2.33E-04
Updated ingestion, general population	4.94E-06	5.30E-06	3.82E-06	4.49E-06	3.92E-06	4.71E-06
Ingestion, subsistence eaters	7.58E-05	8.42E-05	5.84E-05	6.89E-05	5.97E-05	7.14E-05
Updated ingestion, subsistence eaters	3.43E-05	3.80E-05	3.01E-05	3.12E-05	2.71E-05	3.24E-05
Total exposure, general population	1.59E-02	2.40E-02	1.24E-02	2.01E-02	1.28E-02	2.09E-02
Updated total exposure, general	1.53E-02	2.36E-02	1.18E-02	1.95E-02	1.21E-02	2.01E-02
Total exposure, subsistence population	1.87E-02	2.70E-02	1.44E-02	2.24E-02	1.47E-02	2.31E-02
Updated total exposure, subsistence	1.54E-02	2.37E-02	1.18E-02	1.95E-02	1.21E-02	2.01E-02

[a] The highlighted cells reflect the results of the updated analysis; blue highlight indicates the updated cumulative exposures. Unhighlighted from SEHSC (2008b)

[b] Aggregated dermal exposure from application of personal care products / cosmetics evaluated in the Canadian assessment (as surrogate for household cleaners) was included as a conservative estimate of dermal exposure and thus the total adult exposure likely overestimates actual exposure from EPA-regulated products.

[c] Inhalation values reflect only exposure from indoor and outdoor air.

Table 5-14. Summary of exposure estimates for children, mg/kg-bw/day[a]

Children	0-6 months		6 months - 4 years		4 years - 11 years	
Average (mg/kg-bw/d)	**M**	**F**	**M**	**F**	**M**	**F**
Dermal[b]	6.82E-04	2.80E-06	9.98E-03	9.98E-03	2.38E-03	3.04E-06
Inhalation	2.53E-04	2.66E-04	2.37E-04	2.46E-04	1.60E-04	1.44E-04
Updated inhalation[c]	1.96E-05	1.98E-05	2.12E-05	2.03E-05	1.36E-05	1.23E-05
Ingestion, general population	3.98E-03	3.98E-03	2.16E-03	2.16E-03	5.44E-04	5.11E-04
Updated ingestion, general population	3.36E-03	3.36E-03	2.36E-03	3.85E-03	7.33E-05	7.10E-05
Ingestion, subsistence eaters	8.81E-03	8.81E-03	4.25E-03	4.25E-03	1.38E-03	1.34E-03
Updated ingestion, subsistence eaters	3.45E-03	3.45E-03	2.43E-03	2.43E-03	2.42E-03	8.87E-05
Total exposure, general population	1.38E-02	1.42E-02	4.71E-03	4.79E-03	1.16E-03	1.34E-03
Updated total exposure, general	4.06E-03	3.38E-03	1.24E-02	1.39E-02	2.47E-03	8.63E-05
Total exposure, subsistence population	1.86E-02	1.91E-02	6.80E-03	6.88E-03	2.00E-03	2.17E-03
Updated total exposure, subsistence	4.15E-03	3.47E-03	1.24E-02	1.24E-02	4.81E-03	1.04E-04

Children	0-6 months		6 months - 4 years		4 years - 11 years	
90th percentile (mg/kg-bw/d)	**M**	**F**	**M**	**F**	**M**	**F**
Dermal[b]	1.47E-03	8.17E-06	6.13E-03	6.13E-03	7.84E-05	8.87E-06
Inhalation	4.21E-04	4.41E-04	3.96E-04	4.10E-04	2.68E-04	2.40E-04
Updated inhalation[c]	3.31E-05	3.34E-05	3.54E-05	3.39E-05	2.28E-05	2.05E-05
Ingestion, general population	7.61E-03	7.61E-03	4.07E-03	4.07E-03	8.56E-04	8.31E-04
Updated ingestion, general population	5.45E-03	5.45E-03	3.85E-03	3.85E-03	1.49E-04	1.44E-04
Ingestion, subsistence eaters	9.13E-03	9.13E-03	4.83E-03	4.83E-03	1.24E-03	1.20E-03
Updated ingestion, subsistence eaters	5.54E-03	5.54E-03	3.93E-03	3.93E-03	1.76E-04	1.71E-04
Total exposure, general population	2.41E-02	2.46E-02	2.41E-02	5.51E-03	2.02E-03	5.50E-03
Updated total exposure, general	6.95E-03	5.49E-03	1.00E-02	1.00E-02	2.50E-04	1.73E-04
Total exposure, subsistence population	6.18E-02	6.40E-02	6.18E-02	8.44E-03	2.84E-03	3.35E-03
Updated total exposure, subsistence	7.04E-03	5.58E-03	1.01E-02	1.01E-02	2.77E-04	2.00E-04

[a] The highlighted cells reflect the results of the updated analysis; blue highlight indicates the updated cumulative exposures. Unhighlighted from SEHSC (2008b)

[b] Aggregated dermal exposure from application of personal care products / cosmetics evaluated in the Canadian assessment (as surrogate for household cleaners) was included as a conservative estimate of dermal exposure and thus the total adult exposure likely overestimates actual exposure from EPA-regulated products.

[c] Inhalation values reflect only exposure from indoor and outdoor air.

Table 5-15. Inhalation exposure parameters

Route	Parameter	Units	Source	Distribution	Value	Min	Max	Median	Mean	Std	Geo Mean	Geo Std
Indoor air	Conc.	µg D4/m^3 air	Tran and Kannan (2015)	Triangular	0.116	0.00619	0.752	0.116				
	Breathing Rate	m^3/day		Pop Specific; See Breathing Rate worksheet								
	Conversion	µg to mg			1.00E-03							
	Retention Factor	Fraction	Reddy et al (2007)	Constant	10%							
	Equation	(Conc D4 * BR * conversion *retention/BW)										
Outside air	Conc.	µg D4/m^3 air	Yucuis et al (2013)	Triangular	0.054	0.018	0.19	0.054				
	Breathing Rate	m^3/day		Pop Specific; See Breathing Rate worksheet								
	Conversion	µg to mg			1.00E-03							
	Retention Factor	Fraction		Constant	10%							
	Equation	(Conc D4 * BR * conversion *retention/BW)										

Table 5-16. Ingestion exposure parameters

Product	Parameter	Units	Source	Distribu-tion	Value	Min	Median	Max	Mean	Std	Geo Mean	Geo Std	95%
Fish and Shellfish	Amount consumed	g/kg BW/day	CSFII 1994-96, 1998[a]	Custom	pop specific	See Food Intake Distributions Worksheet							
	Conc. of D4	mg/kg of food	Nusz et al 2018	Custom	0.0596								
	Bioavailability	Fraction	Plotzke 1998b	Normal	0.500	0.3704		0.6686	0.5195	0.0497			
	Conversion	g to kg			1.00E-03								
	Equation	(amount consumed * conc*conversion * bioavailability)											
Water	Amount consumed	mL/Day	US EPA 2008, 2011c	Custom	See Water Consumption worksheet								
	Conc. of D4	µg D4/L water	Nusz et al 2018	Constant	0.03								
	Bioavailability	Fraction	Plotzke 1998b	Normal	0.500	0.3704		0.6686	0.5195	0.0497			
	Conversion	µg to mg and mL to L		Constant	1.00E-06								
	Equation	amount consumed * conc*conversion * bioavailability/BW											
Pacifier	Conc	mg D4 /kg product	Zhang et al. 2012	Custom	2.5								
	Product wt	g		triangular	10	9.5	10	10.5					
	Bioavailability	Fraction	Plotzke 1998b	Normal	0.281	0.108		0.4548	0.2814	0.0578			
	Conversion	kg to g			1.00E-03								
	Equation	if in Fraction of pop using (conc*product wt*bioavailablity/BW) else = 0											
	Conc.	µg D4 /kg dirt	Wang 2013b	Custom	8								

Table 5-16. Ingestion exposure parameters

Soil	wt of Soil eaten	mg/day	U.S. EPA 2008 (Child-specific)	Normal Ages 1-7	100									
				Adults	50									
	Bioavailability	Fraction		Normal	0.500	0.3704		0.6686	0.5195	0.0497				
	Conversion	mg to kg in wt of dirt* µg to mg in conc		Constant	1.00E-06									
	Equation	conc*wt of soil eaten*bioavailability/BW												
Subsistence Population Fish and Shellfish	Amount consumed - Adults	g/day	U.S. EPA 2008, 2011	Custom	59				59					170
	Amount consumed- Children	g/day	U.S. EPA 2008	Custom	19.6									
	Conc. of D4	mg/kg of food	Nusz et al 2018	Custom	0.0596									
	Bioavailability	Fraction	Plotzke 1998b	Normal	0.500	0.3704		0.6686	0.5195	0.0497				
	Conversion	g to kg			1.00E-03									
	Equation	amount consumed * conc*conversion * bioavailability/BW												

[a] USDA 1998

Table 5-17. Breathing rate distribution parameters for children and adults							
Population	**Sex**	**Distribution**	**Source**	**Value**	**Min**	**Most Likely**	**Max**
0-6 months	M	Triangular	USEPA (2011)	3.38	2.19	3.38	5.06
	F	Triangular	USEPA (2011)	3.26	2.17	3.26	4.81
0.5 to 4 years	M	Triangular	USEPA (2011)	7.6	5.49	7.6	10.59
	F	Triangular	USEPA (2011)	7.06	5.15	7.06	9.76
4-11 years	M	Triangular	USEPA (2011)	10.59	7.32	10.59	15.22
	F	Triangular	USEPA (2011)	9.84	7.07	9.84	13.76
12-19 years	M	Triangular	USEPA (2011)	17.23	11.19	17.23	25.76
	F	Triangular	USEPA (2011)	13.28	9.00	13.28	19.33
20-59 years	M	Triangular	USEPA (2011)	17.48	12.86	17.48	24.02
	F	Triangular	USEPA (2011)	13.67	9.91	13.67	18.98
60+ years	M	Triangular	USEPA (2011)	12.96	8.89	12.96	18.72
	F	Triangular	USEPA (2011)	9.8	6.24	9.8	14.85

Table 5-18. Custom distributions		
Subsistence Fisherman Children Amount of Fish Consumed		**Data source**
g/day	Percent	Table 10-20 Fish Consumption Among Native American Children (<5 years) Child-Specific EFH (U.S. EPA 2008)
0	21.1	
0.4	0.5	
0.8	0.6	
1.6	2.5	
2.4	0.6	
3.2	3.1	
4.1	3.6	
4.9	1.5	
6.5	2.1	
8.1	11.8	
9.7	1.1	
12.2	2.5	
13	0.5	
16.2	21.2	
19.4	0.5	
20.3	1	
24.3	2.1	
32.4	10.8	
48.6	4.1	
64.8	3.1	
72.9	2.1	
81	1	
97.2	1.1	
162	1.5	
Mean g/day	19.6	
D4 in Silicone Nipple	mg/kg	Zhang et al (2012)
	2.7	
	2.7	
	2.5	
	2.4	
	49	
	9.4	
	4.5	
	0.6	
	1.5	
	0.6	
	2	
Median D4 in silicone nipple	2.5	

Table 5-19. Updated daily total tap water intake distribution by age group

Source: Table 3-30 Tap Water Intake in Breastfed and Formula-fed Infants … at Different Age Points (mL/day) (U.S. EPA 2008)

		Most Likely Value	Mean	SD	Median	P95	Max
Lognormal	<1 year BF	50	130	180	50	525	1172
Lognormal	<1 year NOT BF	440	441	244	440	828	1603
Table 3-29. Total Tap Water Intake (mL/day) for Both Sexes Combined (Exposure Factors Handbook Chapter 3)							
Lognormal	Infants (<1)	240	302	258	240	775	1102
Lognormal	Children (1-10)	665	736	410	665	1516	1954
Lognormal	Teens (11-19)	867	965	562	867	2026	2748
Lognormal	Adults (20-64)	1252	1366	728	1252	2707	3780
Lognormal	Adults (>65)	1367	1459	643	1367	2636	3338

Table 5-20. Measured D4 concentration in environmental media[1]		
Fish (mg/kg)	Water (ug/L)	Soil (ug/kg)
2.36E-01	0.151	11
2.37E-01	0.1615	8
1.44E-01	0.03	8
4.05E-01	0.0087123	8
5.72E-01	0.010873	8
4.40E-02	0.0092313	17
3.77E-02	0.02	8
4.57E-02	0.04	9
4.26E-02	0.0114512	8
1.86E+00	0.425	8
3.48E-01	0.542	8
1.27E+00	0.214	Median = 8
6.92E-03	0.152	
6.61E-03	0.0816	
9.48E-02	0.141	
9.45E-02	0.265	
9.42E-02	0.64	
6.49E-02	0.63	
9.23E-02	0.04	
1.96E-01	0.0783	
1.61E-02	0.146	
8.26E-03	0.04	
7.83E-02	0.05	
8.06E-02	0.065	
1.92E+00	0.05	
1.93E+00	0.03	
1.75E+00	0.03	
1.44E+00	0.02	
1.40E+01	0.02	
6.16E+00	0.02	
3.92E+00	0.02	
3.49E+00	0.0120464	
1.23E-01	0.02	
1.99E+00	0.04	
2.14E+00	0.04	
1.28E+00	0.0126594	
9.30E+00	0.0132912	
2.96E+00	0.0007803	
8.34E+00	0.0032397	
3.89E+00	0.0058415	
4.12E+00	0.0097638	
4.57E+00	0.0082063	
5.99E-02	0.04	
3.31E-02	0.03	

Table 5-20. Measured D4 concentration in environmental media[1]		
3.67E-01	0.04	
1.63E+00	0.0040941	
3.73E+00	0.0053957	
2.58E+00	0.0067575	
2.56E-02	0.05	
1.39E-01	0.06	
6.31E-02	0.055	
1.35E-01	0.05	
2.72E-02	0.06	
6.15E-02	0.04	
6.24E-02	0.0072297	
3.18E-02	0.0014045	
4.04E-02	0.0019071	
5.36E-03	0.0062951	
1.45E-02	0.0103108	
1.07E-02	0.0077123	
1.03E-01	0.003667	
1.65E-01	0.0045234	
8.50E-02	0.0049568	
6.21E-02	0.02	
1.54E-02	0.0139426	
6.65E-02	0.03	
2.48E-01	0.03	
1.60E-01	0.03	
2.08E-02	0.04	
4.35E-02	0.02	
6.49E-02	0.03	
4.35E-02	0.02	
8.33E-02	0.275	
3.98E-02	0.295	
6.58E-02	0.212	
2.15E-02	0.0028084	
1.78E-02	0.0146149	
1.51E-02	0.0023676	
1.45E-02	0.04	
1.29E-02	0.05	
1.25E-02	0.0153089	
1.07E-02	0.06	
2.44E-02	0.102	
3.22E-02	0.04	
8.49E-04	Median = 0.03	
1.07E-03		
1.30E-03		
2.05E-03		
2.55E-03		
2.83E-03		

Table 5-20. Measured D4 concentration in environmental media[1]		
3.11E-03		
2.03E-03		
1.54E-03		
9.34E-01		
3.89E-01		
9.47E-01		
5.89E-01		
6.80E-01		
7.48E-01		
1.14E+00		
1.48E+00		
1.32E+00		
3.58E-01		
2.96E-01		
6.43E-01		
1.79E-04		
4.11E-04		
3.72E-03		
2.29E-03		
6.30E-04		
1.78E-03		
2.41E-01		
1.08E-01		
1.68E-01		
4.25E-03		
2.07E-03		
3.40E-03		
6.55E-02		
4.17E-02		
2.84E-02		
2.85E-02		
9.06E-02		
6.70E-02		
9.84E-02		
5.05E-02		
5.51E-02		
5.44E-02		
8.30E-02		
3.98E-02		
3.62E-02		
3.78E-02		
4.59E-02		
4.86E-02		
1.76E-02		
1.97E-02		
2.60E-02		

Table 5-20. Measured D4 concentration in environmental media[1]		
1.75E-02		
9.74E-03		
2.97E-02		
1.05E-02		
3.37E-03		
6.02E-03		
4.84E-02		
5.85E-02		
5.10E-02		
3.50E-02		
6.27E-02		
2.35E-02		
6.27E-02		
5.28E-02		
3.57E-02		
6.55E-02		
5.34E-02		
5.09E-02		
2.43E-02		
8.71E-02		
2.00E-02		
4.19E-02		
6.92E-02		
5.95E-02		
1.10E-01		
1.47E-01		
1.36E-01		
Median = 5.96E-02		

[1] Concentrations in water and fish from Nusz et al. (2018); concentrations in soil from Wang et al. (2013b)

5.2 Ecological Exposure

This section provides information on the ecological exposure assessment for D4. The approach used incorporates the expected requirements in the Final Rule (*Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act*, 82 Fed. Reg. 33726; U.S. EPA 2017b) and moves beyond the standard deterministic hazard quotient technique to incorporate additional advanced methods for characterizing risk. A conceptual model of D4 release and exposure pathways to ecological receptors, and key sources of information used for this evaluation, are described in Section 4.2.2. Ecological risks to marine, estuarine, and terrestrial ecological receptors are not included in this risk characterization because the highest D4 concentrations have been found in freshwater in urban settings and near industrial wastewater treatment plants. Marine environments would be further from these discharge sources and concentrations of D4 would be lower. Exposure to terrestrial ecological receptors is expected to be much lower than aquatic exposures based on how D4 is produced and used, and its environmental fate properties which minimize persistence in the relevant media. Due to its volatility, D4 released to the atmosphere becomes significantly diluted, and indirect photolytic degradation reduces airborne concentrations further. Therefore, inhalation by terrestrial wildlife or transpiration by terrestrial plants are not considered significant exposure pathways. As discussed in Section 4.2.2, terrestrial ecological receptors could be potentially exposed through deposition of airborne D4 or land application of biosolids (treated sewage sludge from wastewater treatment plants). However, presence of D4 in soil through airborne deposition is expected to be negligible, and accumulation in soil via application of biosolids would not be anticipated due to dispersion, volatilization, and degradation. In addition, it is estimated that <1% of agricultural lands use biosolids as a fertilizer (Lu et al. 2012). Moreover, potential exposures from soil are expected to be low and short-term due to the moderately high binding coefficient of D4 to soil carbon, its tendency to degrade rapidly from dry soils, and its inherent volatility from water and wet soils (Bridges and Solomon 2016; Brooke et al. 2009; Xu and Kropscott 2012; Xu et al. 2014; Xu and Chandra 1999).

Therefore, the goal of the ecological risk characterization is to assess and quantify potential risks to ecological receptors from D4 exposures in freshwater aquatic ecosystems. This assessment was accomplished using distributions, rather than conservative point estimates, of exposure with

measured concentrations of D4 to obtain a realistic view of the probability of harm. This is consistent with EPA's stated intent to "strive to utilize probabilistic approaches for exposure assessments used in a risk evaluation" (U.S. EPA, 2017b).

5.2.1 Release Pathways of D4 into the Environment

The potential release pathways of D4 from industrial and consumer sources into the environment from manufacturing, processing, and formulating facilities (MPFs), and from industrial and consumer end users are discussed in Section 4. The major environmental release pathways for D4 (shown in Figure 4-4, D4 Ecological Risk Conceptual Model) can be categorized as follows:

1. MPF facilities using on-site waste water treatment with direct discharge to a surface water body; these are referred to as "on-site treatment sites," or OT
2. MPF facilities discharging to municipal WWTP, with discharge to a surface water body
3. Down the drain releases from consumer products to a municipal WWTP, with discharge to a surface water body.
4. Subsequent transfer of D4 from the surface water to sediment compartments.

Based on the conceptual model, these release pathways contribute D4 residues to the ecologically-relevant compartments of surface water and sediment. A recent monitoring dataset available for freshwater sites within the U.S. was used to characterize exposure of ecological receptors to D4 in this assessment.

5.2.2 Data Collection

Environmental monitoring data were collected during a U.S. national monitoring program for D4 under an ECA between EPA and a group of five signatory companies. The results of the analyses performed under the ECA provided measured concentrations of D4 in the following media: effluent from MPF facility WWTPs; influent and effluent of municipal WWTPs; biosolids of municipal WWTPs; and surface water, sediment, and biota (benthic invertebrate and fish

species) within the mixing zones of receiving waters. An overview of the sites sampled in the ECA is provided in Table 5-21.

Sites listed in Table 5-21 were sampled twice during 2016, with at least a 3-month interval between the sampling events. All sampling events occurred between April 21, 2016, and December 15, 2016 during low-flow months for the receiving waters. Samples were taken during typical weather conditions and a minimum of three days after a high-flow weather event, e.g., a heavy rainstorm. Surface water, sediment, and biota (i.e., fish and benthic organisms) were collected during both sampling events for all sites. Four MPF sites included in the ECA monitoring program discharge process wastewater into the environment after on-site treatment, referred to hereafter as “on-site treatment sites” or OT sites. Five municipal WWTP sites were monitored as part of the ECA; these WWTPs were selected due to the potential to receive indirect discharge from D4 processors and/or formulators (i.e., D4 reasonably expected in the WWTP influent; these sites are referred to hereafter as “industrial sites”). Upstream processors and formulators were identified through industrial user surveys and other information sources and used to select the WWTPs. Five other municipal WWTP sites selected for monitoring were representative of locations that receive <15% of wastewater from industrial sources and no wastewater from D4 manufacturing or processing (including product formulation) sites; these WWTPs are referred to hereafter as “residential sites.” Additionally, for both the residential and industrial dischargers, WWTP sites were selected based on large discharge rates relative to the receiving body flow rate (low dilution). These WWTP sites had activated sludge treatment with secondary clarification and/or disinfection; additional forms of treatment were not used. A widespread, geographic representation was also a selection criterion for the WWTPs (Table 5-21). The WWTPs selected for the industrial and residential sites were assumed to be representative of the 15,000 to 20,000 municipal WWTPs in the continental United States.

Table 5-21. ECA sampling overview (SEHSC 2016a)

Site Type	Sampling Location	Site ID	Approximate Population Served	Approximate Discharge (cfs)[c]	Average Base Flow[d] (cfs)	Media sampled
Industrial sites (I): municipal WWTPs receiving wastewater from industrial D4 processors or formulators	Iowa City, IA	I1	74,000	11.2	1,510	influent, effluent, and biosolids (from WWTP); **surface water, sediment, benthic organisms, and fish (from mixing zone)**
	Columbus, OH	I2	500,000	139.5	720	
	Wichita, KS[b]	I3	345,000	55.8	485	
	Gresham, OR[b]	I4	106,000	22.3	108,600	
	Chicago, IL[b]	I5	2,292,000	1302	2,415	
Residential sites (R): municipal WWTPs receiving primarily residential waste[a]	Steamboat Springs, CO	R1	13,000	5.6	143	influent, effluent, and biosolids (from WWTP); **surface water, sediment, benthic organisms, and fish (from mixing zone)**
	Boulder, CO	R2	18,000	24.2	23	
	Lexington, KY	R4	143,000	50.2	72	
	Genesee, MI	R5	121,000	55.8	355	
	Elmhurst, IL	R6	42,000	13.0	111	
On-site Treatment sites (OT): D4 MPF sites	Processor, Adrian, MI	OT1	NA	0.1	154	effluent (from WWTP); **surface water, sediment, benthic organisms, and fish (from mixing zone)**
	Manufacturer and formulator, Carrollton, KY	OT2	NA	26	47,000	
	Processor, Friendly, WV	OT3	NA	1674	15,200	
	Manufacturer, processor, and formulator, Waterford, NY	OT4	NA	14.9	6.200	

Notes:
Environmental media considered in the risk characterization are presented in bold font.
[a] Receive less than 15% industrial wastewater and preferably no wastewater influent from D4 processors or formulators.
[b] These sites include two influent locations.
[c] cfs = cubic feet per second
[d] Average monthly flow for period of record 2004-2014 for the base-flow months, where data are available.

Samples were collected for each matrix during each sampling event at each site, including quality control (QC) samples (field spike samples and field blank samples), study samples (field split samples to be analyzed for D4 [one primary sample, one field duplicate sample]),

characterization samples (e.g., for total organic carbon [TOC], percent lipids, etc.), and "retained samples," which were retained by the laboratory until after QA. Most of the environmental matrices were sampled using grab samples with the exception of biosolids and benthic organisms, which were collected using a composite sampling method. Two species of fish were sampled at each location, and when possible, fish samples were from different trophic guilds. Fish samples were composited as necessary to reach the minimum mass needed for analysis.

Table 5-22 shows the D4 and additional sample characterizations performed for each sample type relevant to the ecological assessment (surface water, sediment, biota). Samples were collected as close as reasonably possible to the effluent outfall, within the mixing zone. To verify that sampling occurred within the mixing zone for WWTPs without a National Pollutant Discharge Elimination System (NPDES) permit defined mixing zone, visual observation of the plume, dye tracing, and/or evaluation of temperature-conductivity profiles were performed to verify the mixing zone.

Table 5-22. Sample analysis performed per media type

Media	D4 Concentration basis (dry or wet weight)	Other Sample Characterization Performed						
		Percent moisture	Percent Lipids	Total Organic Carbon	Total Inorganic carbon	Total Carbon	Total Organic Matter	Total Solids
Surface water	NA - µg/L			Y				
Sediment	wet weight	Y		Y	Y	Y	Y	Y
Benthic Tissue	wet weight	Y	Y					
Fish Tissue	wet weight	Y	Y					

Collection of surface water and sediment followed standard EPA collection methods (U.S. EPA 1994a,b, 2001) and included the collection of seven grab samples per sampling event at each location. Of these seven grab samples, there were three investigative samples from each event and location; other samples were collected and analyzed for QA purposes (including splits, field spikes, and "retain" samples that were not analyzed unless a sample was compromised [e.g., bottle broke in transit]). Surface water samples were collected according to a SOP that reflected EPA techniques (U.S. EPA 1994a). Surface water samples were collected as grab samples as opposed to composite samples due to the expected high degree of volatilization of D4 from

aqueous samples. Following surface water collection, samples were immediately transferred to glass bottles with low-density polyethylene square film, polytetrafluoroethylene ("Teflon") lined lids, and Teflon-wrapped threads for closure. Water quality parameters of pH, temperature, conductivity, and dissolved oxygen (DO) were measured at the time of sample collection using a YSI 556 Multiprobe Water Quality Meter.

Sediment sampling locations were collected near surface water sampling locations, except at sites devoid of fine-grained sediment. Three investigative samples per event, at each location, along with QA samples, were also collected for benthic invertebrates, using Ponar dredging and D-frame kick netting or debris picking and sediment vacuum pumps according techniques provided by Powell and Woodburn (2009) and EPA (U.S. EPA 2003a). Sediment samples were collected according to an SOP that reflected EPA techniques (U.S. EPA 1994b, 2001). Sediment sampling locations were a function of bottom substrate type and the availability of fine-grained sediment (i.e., <50% sand-sized particles). Following collection of the sediment by pre-cleaned stainless-steel tools, samples were transferred to labeled polyethylene food storage bags. Each sample was homogenized in its collection bag and transferred to a glass storage jar with a Teflon-lined lid for storage until analysis.

Benthic invertebrate sampling was conducted in parallel with sediment sampling. When necessary to obtain sufficient biomass, collection of benthic organisms continued at alternate locations within the depositional zone (but not beyond 200 m from the effluent outfall) until sufficient mass was obtained. Taxa were counted and identified to the lowest practicable taxon prior to chemical analysis. As required by EPA in the ECA, mussels, clams, and crayfish were not included within the benthic organism sampling (SEHSC 2016a). While these organisms are not typically sensitive to organic chemical exposures (other than pesticides), they should be considered in any future studies. Benthic organism collection continued until a target mass of composited benthic organisms was collected (100 g), which was subsequently divided to prepare the investigative composite benthic samples. To optimize the collection of benthic macroinvertebrates at so many types of streams and rivers, several collection methods were required. Area covered, level of effort, and collection methods sometimes varied between sites.

An attempt was made to sample all available habitats for benthic invertebrates, including macrophytes and organic debris.

For fish, six investigative samples were collected (three samples each from two species, and if possible, from different trophic guilds), along with QA samples. Techniques for sample collection included common seine nets, backpack or boat-mounted electroshocking, gill nets, fyke or hoop nets, and/or rod and reel angling; the fish collections followed procedures provided by EPA (U.S. EPA 2003b, 2011a), Powell and Woodburn (2009) and Zale et al. (2012). Methods were site-specific and selected based on physical, behavioral, environmental, and regulatory factors including water depth, flow rate, habitat, target species, species size, state regulations, and the time of year (Zale et al., 2012). Permits or licenses were obtained for the biological collection at all sites. Trophic guilds were determined according to Page and Burr (1991) and local fish identification guides. Fish were measured (total length) and weighed (wet weight), and a subset of fish at each site was composited for laboratory analysis of D4. At least two species of fish from different trophic guilds were targeted to be sampled at each location, and samples were composited as necessary to reach the minimum mass needed for analysis (i.e. 50 g). For each of the two species, five (n = 5) individual fish (equal to or greater than 50 g each) or five (n = 5) composited samples (sufficient numbers to provide at least 50 g per sample) were collected for analysis. Individual fish were double bagged using polyethylene food storage bags and frozen before shipment. Composited whole-fish samples were placed in glass sample containers and frozen before shipment.

QC and QA procedures were imperative, due to the potential for contamination of samples, and the ubiquity/volatility of D4. QA/QC included collecting representative and unbiased samples of abiotic and biotic media from sites. All sampling and analyses were completed in accordance with TSCA Good Laboratory Practice (GLP) Standards (40 CFR 792); Code of Federal Regulations 2011) to ensure field samples were collected, processed, stored, transferred, and analyzed without cross-contamination. Since D4 is widely present in consumer products, practices were undertaken to avoid the significant potential for sample contamination and volatilization during collection, processing, storage, and analysis. Field and laboratory personnel were required to refrain from using any personal care products that may contain any cyclic

volatile methylsiloxanes (cVMS) materials (e.g., sun-block, sun-screen, hand lotion, antiperspirants, etc.) while preparing for or conducting any activities. Furthermore, vehicles used for field sampling were not cleaned with any products before field activities to avoid cross-contamination from cleaning products containing D4. Further details can be found in the ECA report, attached as Supplemental Information in Nusz et al. (2018).

5.2.3 Analytical Methods and Data Analysis

The samples collected at each site per event are presented in Table 5-23. Details of the analytical methods and data analysis can be found in the ECA report, attached as Supplemental Information in Nusz et al., 2018. A brief discussion is provided here. Once in the laboratory, samples were prepared for chemical analysis. All water samples were extracted in the original sample jars, with the addition of 10 mL of hexane/internal standard solution for the extraction. Sediment samples were homogenized in the sample bags before aliquoting the individual analytical samples. All analyses were performed within the period of stability as identified by the maximum holding times specified in the quality assurance project plan (QAPP) plan. Lab water, reference sediment, and rainbow trout field blank QC samples were analyzed after each event to evaluate whether contamination bias was introduced. Field spike samples were analyzed to evaluate accuracy and potential matrix effects on D4 recovery (Table 5-23). To verify spike recovery concentrations, D4 solutions were spiked into solvent vials containing Internal Standard Working Solution (ISWS) solvent during preparations of field spike QC samples for each matrix. Precision was evaluated by calculating the relative percent difference (RPD) for each pair of field spikes.

Briefly, all samples were extracted with either hexane or tetrahydrofuran (THF). Sample extracts were analyzed using capillary column gas chromatography (GC) with mass spectrometry (MS) detection using electron impact ionization and selective ion monitoring (SIM), or GC/MS-SIM. The D4 in the samples was identified by comparing the retention time and mass spectrum for the sample peak with known D4 reference standards. Finally, D4 was quantified by a stable isotope dilution technique, where the ratio of sample D4 response to an internal standard (^{13}C-D4) was used to minimize matrix effects. A minimum of five points were used in all the calibration curves. Method validation protocols were based on the guidance document Validation and Peer Review of U.S. Environmental Protection Agency Chemical Methods of Analysis (FEM Method

Validation Team 2005), which identifies the need for selectivity, instrument calibration, bias/trueness, precision, quantitation limits and ranges, detection limits, and ruggedness as performance parameters addressed during method validation.

All laboratory analyses were conducted by ALS Environmental laboratory (Kelso, Washington) according to TSCA GLP Standards (40 CFR 792; Code of Federal Regulations, 2011)) and the laboratory's SOPs. The analysis of D4 is not a standard test regularly performed by commercial laboratories. The analytical method for D4 was modified from existing procedures of Knoerr et al. (2017) and Powell and Woodburn (2009, 2010) and validated by ALS/Kelso. The method validation procedure included preparing validation protocols for each matrix, performing the validation work, preparing analytical SOPs, and analyzing performance evaluation samples for each matrix. The method detection limit (MDL) for D4 in each matrix was established based on the validation data and the LOQ was 3× the MDL, while the minimum reportable level for D4 was defined by the lowest calibration standard. MDLs and LOQs for D4, TOC, lipid content, and sediment moisture content for each matrix are presented in (Table 5-24). Before compiling the environmental data, results went through data verification and review for usability (SEHSC 2016b). To combine replicates from a single sampling event, relative percent differences (RPDs) between primary and duplicate D4 concentrations were calculated, and primary and duplicate samples were combined according to the criteria in Table 5-25. For the six benthic organism sampling events for which no duplicate samples were available due to lack of adequate biomass, a single sample was used.

Table 5-23. Investigative and quality assurance samples collected* per site per event

Type of Site	Sample Media	Investigative and QA Samples for D4 Analysis per Site per Event						Investigative and QA Samples for Matrix Characterization per Site per Event			
		No. of Investigative Samples	No. of Investigative D4 Analyses[2]	No. of QA Field Blanks[3] and Field Spikes[4]	No. of QA Solvent Spikes[5]	Total D4 Analyses[6]	No. of Retain Samples	TOC Samples	Lipid Samples	TC/TIC/TOC Samples[7]	LOI Water and TOM Samples[8]
Municipal WWTP [1]											
10 sites, 2 Events	Surface Water	3	6	6	1	13	2	3			
	Sediment	3	6	6	1	13	2			7	7
	Fish (Species 1 and 2)	6	12	4	1	17	4		8		
	Benthic Organisms	3	6	4	1	11	2		5		
On-site Treatment											
4 Sites, 2 Events	Surface Water	3	6	6	1	13	2	3			
	Sediment	3	6	6	2	14	2			7	7
	Fish (Species 1 and 2)	6	12	4	1	17	4		8		
	Benthic Organisms	3	6	4	1	11	2		5		

Notes:
* Not all samples resulted in successful analyses due to insufficient sample size and/or missing characterization data; refer to Table 5-26
[1]These include the WWTPs that received input from industrial users and the residential locations.
[2]Each investigative sample was split two ways and each split were separately analyzed for D4.
[3]Field blanks include lab water, reference sediment, and rainbow trout QA samples.
[4]Field spike QA samples include both unspiked and spiked samples.
[5]Solvent spike results were used to evaluate field spike QA samples.
[6]Total number of samples analyzed for D4.
[7] Total carbon, total inorganic carbon, and total organic carbon.
[8] Loss on ignition, total organic matter.

Table 5-24. Method detection limits (MDLs) and limits of quantification (LOQs) for each matrix and parameter

Matrix	Parameter	Units	MDL	LOQ
Surface water	D4	µg/L	0.02	0.06
	TOC	mg/L	0.08	0.5
Sediment	D4	ng/g wet weight	0.8	2.4
	TOC	%	0.02	0.05
	Water Content	%	NA	0.01
Benthic Invertebrate Tissue	D4	ng/g wet weight	1.9	5.6
	Lipid Content	%	NA	0.01
Fish Tissue	D4	ng/g wet weight	1.9	5.6
	Lipid Content	%	NA	0.01

Notes:
NA = Not Applicable

Table 5-25. Decision criteria for combining duplicate ECA samples

Relative percent difference (RPD)	Relationship to Method detection limit (MDL)	Value used in analysis
<20% different	Both[1] greater than	Mean of primary and duplicate
>20% different	Both greater than	Greater of primary and duplicate
Cannot calculate	One greater than, other less than	Use sample greater than MDL
Cannot calculate	Both less than	Value imputed by censored data analysis

Source: Nusz et al. 2018

[1] Primary sample and duplicate

Concentrations below the MDL were estimated using the regression on order statistics method (Singh and Singh 2013). This method involves fitting a regression line to a normal probability plot of uncensored observations and then imputing values for observations below the MDL in the tail of the assumed normal distribution. After imputing the censored values, D4 concentrations were normalized on a per-sample basis for appropriate sample characterization as follows: D4 concentrations in sediment were normalized for TOC content, and D4 concentrations in fish and benthic invertebrate tissue were normalized for lipid content. Additionally, it was necessary to convert D4 concentrations reported for sediment on a wet weight basis to a dry weight (dwt) basis, using the percent moisture for each sample, to compare to toxicity test results.

The sample sizes of available data from each media type and site that could be adjusted for lipid, TOC, or moisture content are presented in Table 5-26. Out of the 420 unique sampling events designated by the sampling plan, (i.e., 14 sites, 2 sampling events per site, and 3 samples each for water, sediment, and benthic invertebrates, and 6 samples for fish during sampling events), 395 samples were analyzed (combining duplicate samples). Three additional sediment concentration measurements were collected at site R2. Twenty-three benthic invertebrate and five fish samples were not analyzed due to insufficient biomass. Of the 395 samples analyzed, 14 samples were missing lipid, TOC, or moisture measurements, making normalization of these data results impossible; therefore, 381 unique D4 concentrations were used in further analyses after preprocessing (Table 5-26). After results were compiled and preprocessed as described above, cumulative distributions were derived for D4 concentrations measured in water, sediment, benthic invertebrate tissue, and fish tissue using the open source statistical software R1 with the ggplot2 (Wickham 2009) visualization tool.

Table 5-26. Sample sizes of normalized ECA D4 concentrations

Site	Surface Water	Sediment	Benthic Invertebrates	Fish		
Normalized by:	**Not Applicable**	**TOC & Moisture Content**	**Lipids**	**Lipids**		
OT1	6	3	6	12		
OT2	6	6	3	12		
OT3	6	6	4	12		
OT4	6	3	1	12		
I1	6	6	6	12		
I2	6	6	1	12		
I3	6	6	6	12		
I4	6	6	3	9		
I5	6	6	4	12		
R1	6	6	6	12		
R2	6	9	0	9		
R4	6	6	3	12		
R5	6	6	6	11		
R6	6	6	6	12		
Total pre-processing	84	87	61	163	Total	395
Total not able to be normalized	0	6	6	2	Total	14
Total included in the analysis	84	81	55	161	Total	381

Notes:
Site ID defined in Table 5-21.
OT# reflects locations near MPFs with on-site treatment.
I# and R# reflect locations near WWTPs receiving industrial and residential discharges, respectively.
Total not normalized reflects 14 samples that were missing lipid, TOC, or moisture measurements.

5.2.4 Summary of Results from ECA Monitoring Study

Table 5-27 shows the range, median, and 95th percentile values for D4 measured in surface water, sediment, fish, and benthic invertebrates by site type. Individual data can be found in the ECA report, attached as Supplemental Information in Nusz et al. (2018). The results of an additional sampling event performed in July 2017 at one of the on-site treatment locations were

reported to EPA on October 20, 2017 (Flack 2017) are not included in the statistical analysis of the ECA data. However, the concentration of D4 measured in those samples are less than the median concentrations recorded for the site for all media during the ECA Monitoring Study. The 95th percentile values measured in all environmental media collected downstream from on-site treatment sites were higher than media collected downstream from industrial and residential WWTPs. The median concentrations measured in water downstream of on-site treatment sites were higher but of the same order of magnitude as those measured downstream from industrial and residential WWTPs; however, median concentrations measured in tissues and sediments collected below on-site treatment sites were one to two orders of magnitude greater than those collected below municipal WWTPs.

Table 5-27. Summary statistics of D4 concentrations measured in environmental media

Media	Surface Water			Sediment			Fish			Benthic Organisms		
Units	µg/L			ng/g TOC			µmol/g Lipid			µmol/g Lipid		
Site type	On-site Treatment	Industrial	Residential	On-site Treatment	Industrial	Residential	On-site Treatment	Industrial	Residential	On-site Treatment	Industrial	Residential
Number of samples	24	30	30	18	30	33	48	57	56	14	20	21
Min	0.00871[a]	0.00078[a]	0.00140[a]	903	0.00531	0.651	0.000334	4.70E-05	3.69E-06	0.045399	0.000147	1.63E-05
Max	0.640	0.0600	0.295	496000	956	2910	1.05	0.109	0.0232	1.65	0.157	0.0114
Median	0.0800	0.0200	0.0200	7410	48.4	201	0.0693	0.00414	0.00415	0.197	0.00818	0.00276
95th percentile	0.617	0.0578	0.247	446000	610	801	0.626	0.0796	0.0168	1.37	0.0973	0.0103

Notes:
[a] Concentrations of D4 in water are below the MDL values because a number of the results were below detection, and concentrations below the MDL were estimated using the regression on order statistics method (Singh and Singh 2013).

6 Hazard Assessment

6.1 Human Health Hazards

The toxicological database for D4 is extensive. A unique component of this database is the harmonized multi-route PBPK model for both the rat and the human (Gentry et al. 2017).

The D4 toxicological database has been previously reviewed in the peer-reviewed literature as well as by authoritative bodies or regulatory agencies (Table 6-1). The identified key documents were the basis for this human health hazard assessment.

Table 6-1. Publicly available assessments of D4 human health hazard

Peer Reviewed Key Publications	Regulatory and Authoritative Reviews
Dekant *et al* 2017a	Scientific Committee on Consumer Safety (SCCS), 2005; 2010
Gentry *et al* 2017[1]	EC/HC (2008)[1]
Franzen *et al* 2017	REACH Registration Dossier (ECHA, 2019)
Dekant *et al* 2017b	Cosmetic Ingredient Review (CIR), 2009
	UK EA (Brooke *et al*. 2009)[1]
	CSR, 2018
	National Industrial Chemicals Notification and Assessment Scheme (NICNAS), 2016
	Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP), 2005

[1] Included literature review

Literature searches were conducted and included in the peer reviewed literature (Gentry et al. 2017), and for the authoritative and regulatory reviews, specifically by the UK EA (Brooke et al. 2009) and the EC/HC (2008). Therefore, the systematic review conducted pursuant to this risk evaluation limited the literature search dates to 2008–present (see Section 2).

The studies included in the human health hazard assessment were of high quality as concluded by the review publications and regulatory and authoritative reviews. Evaluations of the available data are presented in Franzen et al. (2017), the CSR (2018), and Dekant et al. (2017b). Only studies with a reliability score of 1 or 2, based on Klimisch scores, were included in these assessments and evaluations. In addition, the relevance and quality of new data (post-2008) were also evaluated in the systematic review, as described in Section 2. No new experimental toxicological data that superseded the previously evaluated, high quality studies were found.

Articles presenting additional information relative to mammalian toxicology data and human exposure are described in Appendix C.

Summaries of the key points of the pharmacokinetic, acute toxicity, genotoxicity, and repeated dose (including carcinogenicity and reproductive toxicity) studies are provided in the following sections. Due to the numerous guideline compliant and mechanistic studies in the D4 toxicological database, only the results of key studies are summarized.

6.1.1 Absorption, Distribution, Metabolism and Elimination (ADME)

The toxicokinetics (ADME) of D4 is summarized in the CSR (2018) and evaluated by Franzen et al. (2017). The toxicokinetics of D4 has been evaluated in the human and rat, in *in vivo* and *in vitro* studies via inhalation, oral and dermal routes of exposure. Results from the ADME studies indicate that dermal absorption of D4 is limited, due to its high volatility (dermal absorption value of 0.5% has been identified for D4 (SCCS 2010; CSR 2018; Gentry et al. 2017; EC/HC, 2008). After inhalation exposure, a relatively small amount of inhaled D4 is absorbed systemically (absorption of D4 by inhalation is 8% (CSR 2018)), distributed quickly throughout the body, and readily eliminated through expired volatiles, urine or feces (Franzen et al. 2017). The results from the available studies indicate that D4 has similar kinetics after single and repeated inhalation exposure in rats (Franzen et al. 2017 and Pauluhn 2019). After oral exposure to D4, there is evidence of dose dependent related differences in absorption and metabolism at high doses (300 mg/kg bw/day) compared to lower doses (30 mg/kg bw/day) in rats (Franzen et al. 2017). Additionally, oral absorption varies depending on the vehicle (Gentry et al. 2017; Franzen et al. 2017). Estimates of oral absorption are 52% when D4 is administered in corn oil, 12% when administered in simethicone fluid and 28% when D4 was administered neat (Gentry et al. 2017; EC/HC, 2008).

6.1.1.1 Saturation of Metabolic Capacity

Via inhalation, D4 exhibited saturable hepatic metabolism at dose levels ~300 ppm (Franzen et al. 2017; Sarangapani et al. 2002). Domoradzki et al. (2017b) reports D4 demonstrated dose-dependent kinetic behavior when low (30 mg/kg bw) and high (100 mg/kg bw) oral gavage dose levels were evaluated. Data and modeling results suggest differences in metabolism between

low and high dose administration indicating high dose administration results in or approaches non-linear saturated metabolism (Domoradzki et al. 2017b).

6.1.1.2 Lack of Bioaccumulation

In generic PBPK modeling, highly metabolized, lipophilic compounds with low blood:air partition coefficients do not accumulate systemically or in the blood after repeated exposure (Anderson et al. 2008; Franzen et al. 2017). D4 is a highly metabolized lipophilic compound with a low blood:air partition coefficient. In more detailed PBPK modeling conducted with decamethylcyclopentasiloxane (D5), Anderson et al. (2008) concluded that lipophilic volatile compounds (like D4 and D5) do not accumulate in blood and predictions of the increases in D5 (and D4) in fat with repeat exposures in rats agreed with experiments. Anderson et al. (2008) states that the major characteristic favoring accumulation of volatile chemicals in blood and systemic tissues is poor whole-body clearance, not lipophilicity and that the term bioaccumulation should be used to refer to cases where repeat exposures lead to increases in volatile compounds in blood (or central compartment) concentration. Based on this definition, highly cleared volatile compounds, such as D4 and D5, would not be considered to bioaccumulate on repeat exposures, which is consistent with the pharmacokinetic experimental results. Pauluhn (2019) also concluded “Although some of the physicochemical characteristics speak for bioaccumulation; this is unlikely to occur for a vapor exhaled unmetabolized and fast. This renders sinks to become intermediary storage compartments with limited, if any, likelihood for bioaccumulation”. Pauluhn also concluded “Kinetically, D4 is not expected to bioaccumulate in the blood or systemic tissues due to its rapid clearance by multiple processes (exhalation due to low blood: air partitioning, high hepatic metabolism).”

6.1.2 Acute Toxicity

Acute endpoints from key studies are summarized in Table 6-2. Following acute exposure, D4 poses a low hazard to human health across all routes of exposure (Franzen et al. 2017). The available data indicates that D4 has no potential for adverse effects on the skin or eyes, or as a sensitizer following contact with skin (CIR 2009; SCCS 2010; CSR 2018). Critical reviews and evaluations of the available eye irritation, skin irritation and sensitization studies have concluded that D4 is not a skin sensitizer, or a skin or eye irritant.

Table 6-2. Summary of key studies on acute toxicity endpoints (adapted from CSR 2018)

Method	Endpoint	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from CSR Report)[2]	Reference
Equivalent or similar to OECD Guideline 401 (Acute Oral Toxicity) rat (Wistar) male	Mortality	LD50: > 4800 mg/kg bw	experimental result	Reviewed by CSR18A	2	Löser E (1979)
OECD Guideline 403 (Acute Inhalation Toxicity) rat (Fischer 344) male/female inhalation: aerosol (nose only)	Mortality	LC50 (4 h): 36 mg/l air (male/female)	experimental result	Reviewed by CSR18A	1	Research and Consulting Company Ltd (RCC) (1994)
Equivalent or similar to OECD Guideline 402 (Acute Dermal Toxicity) rat (Wistar) male/female	Mortality	LD50: > 2.5 ml/kg bw (male/female)	experimental result	Reviewed by CSR18A	2	Ramm W (1985)
Equivalent or similar to OECD Guideline 404 (Acute Dermal Irritation / Corrosion) rabbit (albino) Coverage: (shaved)	Skin irritation	Not irritating	experimental result	Reviewed by CSR18A	2	Pasquet, J (1971)
OECD Guideline 405 (Acute Eye Irritation / Corrosion) rabbit (New Zealand White)	Eye irritation	Not irritating Cornea score: 0 of max. 0 (mean) (Time point: 24/48/72h) Iris score: 0 of max. 0 (mean) (Time point: 24/48/72h)	experimental result	Reviewed by CSR18A	2	Bayer Institute of Toxicology (1979)
OECD Guideline 406 (Skin Sensitization) guinea pig (albino) female Induction: intradermal and epicutaneous Challenge: epicutaneous, occlusive	Skin sensitization	Not sensitizing No. with positive reactions: 1st reading: 0 out of 20 (test group); 48 h after challenge; dose: 10% 1st reading: 0 out of 10 (test group); 48 h after challenge; dose: 100% 1st reading: 0 out of 10 (negative control); 24 h after challenge; dose: 10% or 100%	experimental result	Reviewed by CSR18A	1	Schmidt WM (1985)

[1] Human health studies include a range of possible scores between 21 and 84 for animal toxicity, and 23 and 92 for in vitro studies. A higher score indicates a higher unreliability.
[2] CSR 2018 (CSR18A)

6.1.3 Genotoxicity

Data presented in Table 6-3 show that D4 has no potential for genotoxicity. Studies in bacteria or mammalian cells (*in vitro* chromosomal aberration and sister chromatic exchange assays) indicate D4 is not genotoxic. *In vivo* studies (micronucleus and dominant lethal assay) also indicate D4 is not genotoxic.

Table 6-3. Summary of key studies on genotoxicity (adapted from CSR 2018)

Method	Endpoint	Results	Remarks	Evaluation (score based on review)[1]	Klimisch score (from CSR Report)[2]	Reference
OECD Guideline 471 (Bacterial Reverse Mutation Assay) (1983) USEPA Fed Reg 50, 51, 51 (1987) S. typhimurium, other: TA98, TA100, TA1535, TA1537, TA1538 (metabolic activation: with and without)[3]	Gene mutation	Negative with and without metabolic activation Test results: negative for Salmonella typhimurium all strains tested; metabolic activation: with and without; cytotoxicity: no, but tested up to limit concentrations	Doses: 0.0003 - 5.0 mg/plate (10 concentrations, cytotoxicity test); 0.1-5.0 mg/plate (5 concentrations, mutagenicity test) experimental result	Reviewed by CSR18A	2	Vergnes J (1993a) Vergnes *et al*. (2000)
Equivalent or similar to OECD Guideline 476 (In vitro Mammalian Cell Gene Mutation Test) Mouse lymphoma L5178Y cells (met. act.: with and without)	Gene mutation	Negative (with and without activation) Test results: negative for mouse lymphoma L5178Y cells (all strains/cell types tested); metabolic activation.: with and without; cytotoxicity: yes (at 50 µg/ml)	Doses: 0.0032 - 0.05 µl/ml. equivalent to 3.2-50 µg/ml experimental result	Reviewed by CSR18A	2	Litton Bionetics (1978) Isquith *et al*. (1988a)
USEPA health effects testing Guideline 50 (188) 40 CFR part 798 Equivalent or similar to OECD Guideline 473 (In vitro Mammalian Chromosome Aberration Test) Chinese hamster Ovary (CHO) (met. act.: with and without)	Chromosome aberration	Negative (with and without activation) Test results: negative for Chinese hamster Ovary (CHO)(all strains/cell types tested); metabolic activation.: with and without; cytotoxicity: yes (0.01 mg/ml without activation, 0.003 mg/ml with activation)	Doses: 0.0003 - 0.01 mg/ml, (without activation) 0.003 - 0.03 mg/ml (with activation) experimental result	Reviewed by CSR18A	2	Vergnes J (1993b) Vergnes *et al*. (2000)
Equivalent or similar to OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test), *in vivo* Rat (Sprague-Dawley) male/female Inhalation	Chromosome aberration	Negative Genotoxicity: Negative (male/female); toxicity: no effects (in bone marrow)	0, 720 ppm (actual mean) (analytical conc.) experimental result	Reviewed by CSR18A	2	Vergnes *et al*. (2000)
Equivalent or similar to OECD Guideline 478 (Genetic Toxicology: Rodent Dominant Lethal Test) , *in vivo* Rat (Sprague-Dawley) male/female Oral: gavage	Chromosome aberration	Negative Test results: Genotoxicity: Negative (male/female); toxicity: no effects	0, 100, 500, and 1000 mg/kg/day (actual ingested (by gavage of gas chromatographically analyzed test substance)) experimental result	Reviewed by CSR18A	2	Isquith A *et al., (*1988b)

[1] Human health studies include a range of possible scores between 21 and 84 for animal toxicity, and 23 and 92 for in vitro studies. A higher score indicates a higher unreliability.
[2] CSR 2018 (CSR18A)
[3] Metabolic activation with and without the use of S9 fraction that is made from organ tissue homogenate.

6.1.4 Repeated Dose Toxicity

Repeated dose toxicity studies are available for the inhalation, dermal, and oral routes of exposure. The key studies are summarized in Table 6-4.

The key study, as identified by CSR (2018) and Dekant et al. (2017b), used to assess the repeated dose inhalation toxicity of D4 is the combined repeated dose and carcinogenicity whole body vapor inhalation study in rats (Jean and Plotzke 2017). Inhalation exposure of rats to D4 up to 700 ppm increased the absolute and/or relative kidney weights and resulted in a significant increase in chronic nephropathy in both sexes of rats exposed for two years (lowest-observed-adverse-effect concentration [LOAEC] = 700 ppm, no-observed-adverse-effect concentration [NOAEC] = 150 ppm). Chronic progressive nephropathy (CPN) is a spontaneous degenerative disease in the commonly used strains of laboratory rats, and its incidence and severity are frequently exacerbated by chronic administration of chemicals (Hard *et al*., 2013). While the underlying initial events of CPN in rats are not well defined, the available evidence indicates that CPN is a distinctive disease entity in rats that has no human counterpart based on clinical manifestation, disease progression, and influencing factors. Therefore, the kidney effects observed after chronic inhalation of D4 at the highest concentration of 700 ppm likely have no relevance for human risk characterization (Hard et al. 2013).

No toxicity was observed up to the highest dose tested in a 28-day dermal toxicity study (no-observed-adverse-effect level [NOAEL] ≥ 960 mg/kg; Bayer AG 1988). Decreased body weight was reported in a 14-day oral toxicity study in rats (Dow Corning Corporation 1990; lowest-observed-adverse-effect level [LOAEL] 1600 mg/kg based on decreased body weight, NOAEL = 400 mg/kg). Changes in liver weights without corresponding adverse histopathological or clinical chemistry findings at 400 and 1600 mg/kg in this study are considered to be adaptive, non-adverse effects (Dow Corning Corporation 1990).

Table 6-4. Summary of key studies on repeated dose toxicity (taken from CSR 2018)

Method	Endpoint	Results	Remarks	Evaluation (score based on review)[2]	Klimisch score (from CSR Report)[3]	Reference
USEPA OPPTS 870.4300 (Combined Chronic Toxicity / Carcinogenicity) equivalent or similar to OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies) Rat (Fischer 344) male/female (inhalation: vapor) (whole body)	Repeated dose toxicity - inhalation	NOAEC: 150 ppm (male/female) LOAEC = 700 ppm (male/female) based on chronic nephropathy	10, 30, 150, and 700 ppm (nominal conc.) Vehicle: clean air Exposure: Up to 24 months (6 hours/day, 5 days/week) Kidney effects observed after chronic inhalation of D4 at the highest concentration of 700 ppm likely have no relevance for human risk characterization (Hard et al. 2013).	Reviewed by CSR18A Dekant *et al*., 2017b	1	Batelle (2004) Jean and Plotzke 2017
Equivalent or similar to OECD Guideline 410 (Repeated Dose Dermal Toxicity: 21/28-Day Study) Rabbit (New Zealand White) male/female Subacute	Repeated dose toxicity - dermal	NOAEL: >= 1 ml/kg bw (male/female)	0.1, 0.3, 1 ml/kg bw (96, 190, 960 mg/kg bw) Exposure: 3 weeks (5 days/week)	Reviewed by CSR18A	2	Bayer AG (1988)
Non-guideline range-finding study for oral repeated dose toxicity rat (Sprague-Dawley) male/female subacute (oral: gavage)	Repeated dose toxicity - oral	NOAEL: 400 mg/kg bw/d (male/female) LOAEL: 1600 mg/kg bw/day (male/female) based on decreased body weight	0, 25, 100, 400 or 1600 mg/kg bw/d Exposure: 14 days	Reviewed by CSR18A	2	Dow Corning Corporation (1990)

NOAEC = no observable adverse effect concentration
NOAEL = no observable adverse effect level
LOAEC = lowest observable adverse effect concentration
LOAEL = lowest observable adverse effect level

6.1.5 Carcinogenicity

The key carcinogenicity study is summarized in Table 6-5. In the combined repeated dose and carcinogenicity study in rats (Batelle 2004; Jean and Plotzke 2017), an increase in the incidence of endometrial epithelial hyperplasia and a significant positive trend for the incidence of benign endometrial adenomas was reported at the highest concentration tested (LOAEC = 700 ppm). A NOAEC of 150 ppm for D4 was determined for the uterine endometrial adenomas and hyperplasia in the female rats (Jean and Plotzke 2017). The incidence of uterine adenomas alone was not increased compared to concurrent controls and uterine adenomas are a common tumor in aging female Fischer 344 rats (Jean et al. 2017).

Dekant et al. (2017a,b) evaluated the mode of action (MoA) of uterine effects in rats and the human relevance of the effects. Mechanistic studies suggested that the endometrial tumors arise because D4 may act as a dopamine agonist (Brooke et al. 2009; SCCS 2005). By maintaining dopaminergic inhibition of prolactin secretion, female reproductive senescence is delayed, which leads to prolonged stimulation of the endometrium and eventually to tumors. Differences in the reproductive ageing process between humans and rodents render this mechanism irrelevant to humans (Brooke et al. 2009) The available data suggest that the observed benign tumors are not relevant to humans (Brooke et al. 2009; SCCP 2005). D4 is not genotoxic and there was no appreciable direct hormonal activity of D4 demonstrated. Therefore, the induction of the endometrial effects observed in the two-year inhalation study are likely due to interferences of D4 with rat estrous cycle control that are only seen at doses that exceed the metabolic capacity of animals (≥300 ppm) and are not relevant to women (Dekant et al. 2017a,b; Franzen et al. 2017). In addition, the recent review by Pauluhn (2019) has suggested that interferences of D4 with rat estrous cycle control may be secondary to high concentrations (≥Vsat) causing physical sensory stimuli phenotypically manifested as rodent (rat)-specific adaptive (nociceptive) changes rather than human-relevant adversities. This hypothesis is currently being explored by the Silicone Industry and is discussed further below in section 6.1.8.

Table 6-5. Summary of key studies on carcinogenicity (adapted from CSR 2018)

Method	Response	Results	Remarks	Evaluation (score based on review)[2]	Klimisch score (from CSR Report)[3]	Reference
USEPA OPPTS 870.4300 (Combined Chronic Toxicity / Carcinogenicity) equivalent or similar to OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies) Rat (Fischer 344) male/female (inhalation: vapor) (whole body)	Carcinogenicity	NOAEC (carcinogenicity): 150 ppm (female) LOAEC (carcinogenicity): 700 ppm (female) based on increased uterine weight, increased incidence of endometrial cell hyperplasia, and an increased incidence of endometrial adenomas NOAEC (carcinogenicity): >=700 ppm (males)	10, 30, 150, and 700 ppm (nominal conc.) Vehicle: clean air Exposure: Up to 24 months (6 hours/day, 5 days/week) key study experimental result	Reviewed by CSR18A Dekant *et al*., 2017b	1	Batelle (2004). 24-Month combined chronic toxicity and oncogenicity whole body vapor inhalation study of D4 in Fischer 344 Rats. Testing laboratory: Batelle, Toxicology Northwest, 900 Battelle Blvd, PO Box 999, Richland, WA 99354. Dow Corning Internal Report no.: 2004-I0000-54091 (2004-SSRP-2429). Report date: 2004-08-16.

6.1.6 Reproductive and Developmental Toxicity

Table 6-6 provides a summary of the key reproductive and developmental studies for D4. Reproductive effects in rodents following inhalation exposure were reported in the toxicological database for D4 and included: impaired fertility and reductions in the numbers of corpora lutea, implantation sites and litter sizes. Based on the results of mechanistic studies (Dekant et al. 2017a,b; Brooke et al. 2009), the MoA for the reproductive toxicity of D4 in rodents is the induction of a delay or blockage of the luteinizing hormone (LH) surge necessary for optimal timing of ovulation in rodents. An insufficient or blocked pre-ovulatory LH surge fails to induce or delays ovulation in the rat and results in the fertility effects as demonstrated with D4 (impaired fertility, reduction in the number of corpora lutea, implantation sizes and litter sizes). This MoA is unlikely to be relevant to humans (Plant 2012; Dekant et al. 2017a,b) based on the qualitative and quantitative differences between rat and human in estrous cyclicity and neural/hormonal regulation of ovulation in humans. Furthermore, the reproductive effects following D4 exposure were only seen at the two highest dose levels (500 and 700 ppm). It is possible that these doses may have exceeded the rat physiological capacity to handle the chemical thereby further calling into question the relevance of this effect in humans and/or as discussed by Pauluhn (2019) that these effects are secondary to the presence of mixed aerosol vapor at these higher exposure concentrations with subsequent physical sensory stimuli phenotypically manifested as rodent (rat)-specific adaptive (nociceptive) changes rather than human-relevant adversities. As a conservative endpoint, a NOAEC of 300 ppm was identified from the rat reproductive studies with a LOAEL of 500 ppm (Gentry et al. 2017).

No effects on embryotoxicity or developmental toxicity (teratogenicity) were reported in developmental toxicity studies in rats or rabbits by the inhalation route (International Research and Development Corporation 1993a,b; York and Schardein 1994). Maternal toxicity was reported at 500 ppm in rabbits based on reduced food consumption and at 700 ppm in rats based on reduced food consumption and body weight (NOAEC for both rabbits and rats = 300 ppm).

Table 6-6. Summary of key studies on reproductive and developmental toxicity (adapted from CSR 2018)

Method	End Point	Results	Remarks	Evaluation (score based on review)[2]	Klimisch score (from CSR Report)[3]	Reference
USEPA OPPTS 870.3800 (Reproduction and Fertility Effects) equivalent or similar to OECD Guideline 416 (Two-Generation Reproduction Toxicity Study) rat (Sprague-Dawley) male/female two-generation study inhalation (whole body)	two-generation rat reproduction study	NOAEC reproductive effects (all): 300 ppm (male/female) LOAEC reproductive effects: 500 ppm based on reductions in mean live litter sizes and mean number of pups born were observed in the 500 and 700 ppm D4 groups for the F0 animals, and statistically significant reductions were noted for the first mating period in the F1 animals for the mean live litter size in the 500 and 700 ppm groups and for mean number of pups born in the 700 ppm group NOAEC (P): 300 ppm (male/female) LOAEC (P): 500 ppm based on reductions in body weight gains at 500 ppm)	70, 300, 500 and 700 ppm (nominal conc.) 71, 298, 502 and 700 ppm (analytical conc. F0 generation) 71, 301, 502 and 702 (analytical conc, F1 generation) Exposure: Exposure period: F0 and F1 males and females were exposed at least 70 days prior to mating, throughout mating, gestation (to gestation day 20), lactation, with the exception of lactation days 0-4, until euthanization. Starting on PND 22, F1 weanlings were exposed to D4 as described for the F0 generation. The F2 pups were not directly exposed to D4. Duration of test: approx. 39 months (6 hr/day, 7 days/week)	Reviewed by CSR18A Dekant *et al*., 2017b	1	WIL Research Laboratories, Inc (2001) Siddiqui, WH, DG Stump, KP Plotzke, JF Holson, and RG Meeks (2007)
Equivalent or similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study) Rat (Sprague-Dawley) Inhalation (whole body)	Developmental Toxicity	NOAEC (maternal toxicity): 300 ppm based on reduced food consumption and body weight at the LOAEC of 700 ppm) NOAEC (teratogenicity): >= 700 ppm	100, 300, 700 ppm (nominal and actual conc.) Exposure: day 6-15 of gestation (daily for 6 h) key study experimental result	Reviewed by CSR18A	1	International Research and Development Corporation (1993b) York R, Schardein JL (1994)
Equivalent or similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study) Rabbit (New Zealand White) Inhalation (whole body)	Developmental Toxicity	NOAEC (maternal toxicity): 300 ppm based on reduced food consumption at the LOAEC of 500 ppm NOAEC (teratogenicity): >= 500 ppm	100, 300, 500 ppm (nominal conc.) 100, 300, 501 ppm (analytical conc.) Exposure: day 6 - 18 of gestation (daily for 6 h) key study experimental result	Reviewed by CSR18A	1	International Research and Development Corporation (1993a) York R, Schardein JL (1994)

6.1.7 Estrogenic / Progesterone Receptor Effects

The affinity of D4 for the estrogen and progesterone receptors is low to non-existent as determined in various *in vitro* and *in vivo* studies based on the review of the available data (Franzen et al. 2017; Dekant et al. 2017a,b). Dekant et al. (2017a) concluded that "it is unlikely that the very weak activity of D4 in estrogenic assays is responsible for the increase in the endometrial proliferative lesions seen in the two-year chronic bioassay." As further support, Dekant et al. (2017a) state that there were no reported indications of estrogenic or anti-estrogenic effects in male rats, in estrogen-sensitive tissues in females, or in hormone-related developmental landmarks, including anogenital distance in rat pups in a two-generation reproductive developmental study with D4. Borgert et al. (2018) demonstrated that the potency of D4 is one to two orders of magnitude below the minimum required for activity via the estrogen receptor in humans. Available USEPA ToxCast evaluations of D4 indicate no potential for estrogenic or androgenic effects (USEPA 2019). The results of USEPA ToxCast Pathway Model for estrogen receptor and androgen receptor agonist or antagonist effects are 0.0 for all endpoints (USEPA 2019).

6.1.8 Additional Information and Ongoing Work on Reproductive/uterine Effects in Rodents

As discussed above, reproductive/uterine effects in rodents were reported in the toxicological database for D4 (Siddiqui et. al. 2007; Jean and Plotzke 2017). D4 is known to attenuate the LH surge in rats resulting in the reduced mean litter size (Quinn et. al. 2007). The specific mechanism for attenuating the LH surge is not known. Dekant et al. (2017b) conducted a QWoE on the potential modes of action responsible for both the reproductive effects and the uterine effects seen in the chronic bioassay study with D4. The QWoE methodology was applied to two possible modes of action scenarios to assess their experimental support and to evaluate the human relevance of the best supported MoA. The competing scenarios propose molecular initiating events based either on dopamine – like activity by D4 or estrogenicity of D4. The chain of key events for these competing scenarios and their scores were outlined and assessed in the publication. The authors not only acknowledge that although experimental work has been undertaken to assess the MoA, no molecular initiating key event has been identified for either the reproductive effects or the uterine effects, but also hypothesize the two effects could be

interrelated. The D4 mechanistic studies are more complicated since some endpoints may be confounded by experimental conditions (difficulty with the D4 concentration being maintained *in vitro* and achieving higher concentrations *in vivo*) and good *in vitro* models for some proposed molecular initiating/key events are not available. It is also possible that there is no molecular initiating event and that both the effects seen in the reproductive studies and the chronic bioassay are secondary to a nonspecific effect or toxicity following a high exposure to D4.

The following discussion summarizes potential nonspecific effects or MoAs that are currently under investigation by the Silicone Industry and that may play a role in downstream effects such as the reproductive effects and the uterine effects seen following inhalation exposure to D4.

First, it is important to note that the uterine effects were only seen following exposure to the highest exposure concentration of D4 (700 ppm) and the reproductive effects were only seen at the top two doses (500 and 700 ppm). In addition, at air concentrations of D4 greater than ~300ppm, Sarangapani et. al. 2002 reported that there was an apparent saturation of liver enzymes with subsequent decreasing liver metabolism suggesting that the high doses of D4 may exceed the physiological ability of the rat to handle the chemical. This is a consequence of a standard regulatory toxicological testing approach of driving exposure concentrations to unrealistically high doses to determine the maximum tolerated dose (MTD). When adverse effects are only seen at high doses, it is important to understand the role that nonspecific effects or toxicity may play in initiating these adverse effects which would then be considered as secondary to a nonspecific toxicity.

Areas of current exploration are further discussed below. These investigations have not yet been published.

6.1.8.1 Alterations of Membrane Microviscosity

One proposed way that non-specific effects can occur is through alterations in membrane microviscosity or membrane fluidity. Examples of hormone induced changes in membrane microviscosity have been shown (Strulovici et al. 1981; Torres et al. 2017) and changes in

membrane microviscosity can be caused by endogenous and exogenous chemicals (Jetten et al. 1982; Meeks et al. 1981).

A dopamine-like -related MoA was considered for reproductive outcomes following inhalation exposure to D4 (Dekant et al. 2017a). However, after a review of the results from a series of *in vivo* and in *vitro* studies to evaluate the ability of D4 to stimulate/block prolactin release *in vivo* and from specific cells *in vitro* and evaluate D4's affinity for dopamine receptors, the authors concluded that it is unlikely for D4 to interact directly with dopamine receptors. Although both the *in vivo* and *in vitro* studies demonstrated reduced prolactin release following D4 exposure, a direct interaction of D4 with dopamine receptors was not established (Thackery, 2009; Baker, 2010; Domoradzki, 2011). The authors indicated more subtle changes in the pathway following exposure to D4 may suggest an indirect interaction with the dopamine pathway distal to the receptor and may be related to a non-specific mechanism of cycle disruption derived from inhalation exposure to high vapor/aerosol concentrations of D4.

To investigate this further, studies have been performed to assess D4's ability to alter membrane fluidity and possible consequences of this alteration (Iontox 2018). Initially, it was shown that D4 could alter the fluidity of liposome bilayers and that D4 could alter the membrane fluidity of rat primary pituitary cells *in vitro*. Subsequently, using rat primary pituitary cells, 24 hours of incubation also resulted in a dose-dependent decrease in prolactin production. Finally, increasing concentrations of D4 disrupted prolactin release up to 42%, a similar decrease to that observed with dopamine and previously reported (Dekant et al. 2017a). The mechanism by which D4 inhibits the release of prolactin, appears related to changes in membrane microviscosity. This conclusion is based in part on the observations that dopamine is more potent and produces a greater maximal response as compared to D4, D4 does not bind to the dopamine receptor and that the D4 inhibitions of prolactin release occurred within the same concentration range of altered membrane fluidity previously demonstrated in rat immortalized pituitary cells (to be confirmed with ongoing work). This is consistent with the previous work that concluded the inhibition of prolactin release observed *in vivo* and *in vitro* is not likely due to dopamine receptor agonism as D4 has not been shown to be a dopamine receptor agonist (Dekant et al. 2017a). A likely mechanism is a change in membrane fluidity that could lead to

changes downstream of the receptor generating similar type of outcomes but mediated by a non-specific and reversible membrane disruption (Iontox 2019) that would only occur at high unrealistic exposures in a laboratory setting and may be secondary to tissue specific nonlinear dose differences as a result of unsuspected aerosol-phase exposures that may have taken place during the D4 inhalation studies (Pauluhn 2019).

6.1.8.2 Expert Review of D4 Inhalation Exposure

A second pathway for non-specific toxicity has emerged following an expert review recently completed by Prof. Dr. Jürgen Pauluhn, EU-Registered Toxicologist, DABT (retired) of the D4 inhalation toxicology (Pauluhn 2019).

It appears that the inhalation toxicity of D4 follows the generic principles of a volatile lipophilic and surface-active substance with differing properties in its vapor and liquid aerosol phase. Accordingly, the NOAEL of inhalation studies seems to be more contingent on the physicochemical properties than any typical 'intrinsic' toxicity of D4. The low inhalation toxicity of D4 requires inhalation testing exceeding the concentrations where the vapor phase can easily be maintained. Dr. Pauluhn's conclusion is that the technically challenging conditions necessary to achieve higher exposure concentration of D4 make it increasingly difficult to study vapor phase in the absence of metastable aerosol. The author suggests this issue is leading to difficulty in distinguishing unequivocal adversities from an adaptive high-dose phenomena.

In summary, all studies seem to reveal a unifying phenomenon; namely, that at high concentrations (e.g., the effect levels seen in the D4 repeated dose studies) the aerosol-phase predominates the vapor-phase. The former may cause physical sensory stimuli phenotypically manifested as rodent (rat)-specific adaptive changes rather than classical adversities. Apart from rodent-specific secondary and sensory stressors-related phenomena, the inhalation toxicity of D4 was shown to be acute and non-cumulative in nature.

Dr. Pauluhn's review of the reproductive studies (Siddiqui et al., 2007), where reproductive effects were only seen at 500 and 700 ppm concluded higher variability with an overall trend to increased aerosol concentrations at exposure concentrations of 500 and 700 ppm (Figure 6-1).

From the relationships given in Figure 6-1, one may conclude that aerosol- or peak concentration (Cmax)-related artifacts can be excluded at ≤300 ppm and may substantially affect the outcome at the higher concentrations of 500 and 700 ppm.

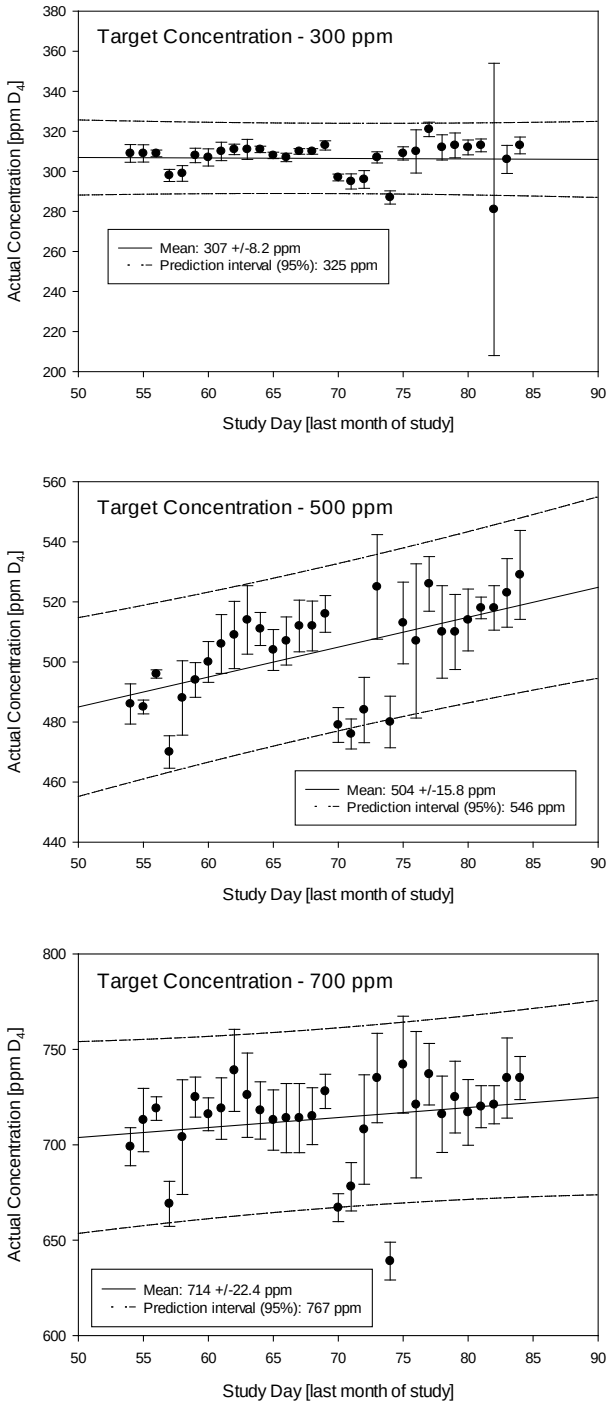


Figure 6-1. Actual concentration (10 per 6-h exposure day) during the last month of study (means±S.D.) WIL reprotoxicity study.

Table 6-7 provides a summary of the various inhalation studies reviewed and an assessment of vapor vs aerosol generation in these studies.

Table 6-7. Overview of repeated exposure inhalation studies and inhalation chamber variables that may affect the liquid aerosol to vapor phase relationship

Study	Temperature(°C) (Mean±SD[a])	V_{sat} (ppm) Range	Conc. (ppm)Vapor	Conc. (ppm) Aerosol	Conc. (ppm) Aerosol &Cmax
RCC: 4-wk NO/Neb	20.6±0.5 (19.2-21.0)[c]	800-1000	200(-)	450(±) 740(+) 1130(++)	-
TCC: 13-wk NO/Neb	20.7±1.2	800-1000	35(-) 125(-)	500(+) 900(++)	-
WIL: Repro WB/Vap2	25±0.9	1300-1400	70(-) 300(-)	500(+++) 700(+++)	500(+++) 700(+++)
Battelle: 2-year WB/Vap3	23.4 (20-27)[c]	800-1500	10(-) 30(-) 150(-)	700(+)	-

Abbreviations: V_{sat}: vapor saturation, NO-nose-only, WB-whole body, wk-week, a) Maximum SD from all groups, b) Nominal concentration was given preference. Neb-Hospitak 950 nebulizer, Vap1: Piston pump & J-tube maintained at 90-110°C, Vap2: liquid D4 was metered into a vaporization column maintained at 85-95°C, Vap3: Battelle in-house built vaporization device, c) minimum – maximum range. The scoring system used in Table is as follows: '±': presence of aerosol cannot be excluded, '-': 'exposure to the aerosol-free vapor phase' expected, '+': 'residual (large) aerosol likely to be present', '++': 'stable aerosol present', '+++': 'aerosol + peaks' expected.

It is important to note that although the above studies often concluded they were able to maintain vapor exposure; Dr. Pauluhn's assessment concluded that fluctuating concentrations cannot be detected by the method of sampling applied in these studies.

With exposure to cVMSs at concentrations high enough to evoke physical interactions, rodent-specific nociceptive, i.e., sensation-related, stimuli can be expected. These types of sensory events commonly occur concentration-dependently. The stimulation of this system causes neuronal mechanism-triggered stresses with somatizations, typically confounded with systemic toxicity on stress-susceptible organs, such as adrenals, thymus, and gonads. Recognizing the high lipophilicity of the liquid aerosol phase of D4, liquid or vapor phase partition will occur within the lipophilic membranes of the sensory nociceptive nerves present in the nasal airways. Small laboratory nocturnal rodents respond to stress by activating a wide array of behavioral and physiological responses that are collectively referred to as the stress response (Smith et al., 2006). It is reasonable to assume that substances capable of causing sensory perturbations may stimulate the corticotropin releasing factor (CRF) which plays a central role in the stress response by regulating the hypothalamic-pituitary-adrenal (HPA)-thymic axis. In response to

stress, CRF initiates a cascade of events that culminate in the release of glucocorticoids from the adrenal cortex. Elevations in glucocorticoids can inhibit reproductive neuroendocrine activity in a variety of species, ranging from rodents to primates and domestic animals leading to cycle disruption and decreased LH release.

The Silicone Industry is in the process of evaluating the possible conduct of follow up studies to assess if high concentrations of D4, with likelihood of an aerosol-phase predominating, is leading to a rodent-specific sensory stressors-related phenomena or tissue specific nonlinear dose differences that may be playing a role in the reproductive and uterine effects only seen at high concentrations. If the reproductive/uterine effects are secondary to this rodent-specific sensory stressors-related phenomena or a result of tissue specific nonlinear dose differences leading to a nonspecific change in membrane fluidity in the tissue area that control LH surge, these effects would be considered a secondary nonspecific toxicity and not relevant to humans.

6.1.9 Physiologically-based Pharmacokinetic (PBPK) Modeling

PBPK modeling is a valuable tool that arose from the recognition that concentrations of chemicals at target tissues are more predictive of biological responses than are external doses (Tan et al. 2018; USEPA 2006; WHO 2010). PBPK modeling represents the best available science and is important in assessing the potential effects on human health and also in establishing the most appropriate POD for use in human health risk assessment. Because of the specific pharmacokinetic behaviors of D4 including high lipophilicity, high volatility with low blood-to-air partition coefficients and an extensive metabolic clearance as well as elimination by exhalation that regulates tissue dose after exposure, the use of a PBPK model provides a dose metric that reflects these processes. The characterization of the potential for adverse effects after exposure to D4 based on an internal dose metric removes the subjective application of varying uncertainty factors and allows examination of the differences between internal dose metrics associated with exposure and those associated with adverse effects.

Campbell et al. (2017) published a refinement of the oral exposure description in the cyclic siloxane PBPK model originally published by McMullin et al. (2016). This PBPK model is the one that was utilized in the risk evaluation by Gentry et al. (2017). Specifically, Campbell et al.

(2017) refined the model to include representation of rat kinetic data in plasma, tissues, and exhaled breath for D4 after oral bolus administration. Additional refinements were made for hepatic induction of metabolism in the liver and allometric scaling of rate constants for the deep tissue compartments which according to the authors will allow the refined PBPK model to be used in uncertainty analysis. Further, the authors stated that the refined PBPK model was able to reproduce D4 kinetic data after inhalation exposure (rat and human) or dermal exposure (human).

Gentry et al. (2017) stated that pharmacokinetic data for D4 are sufficient for the development of a multi-route PBPK model. Further update and refinement of this multi-route PBPK model is underway and expected to be submitted for publication in early 2020. This model update will include a conversion of the model from asclX to the R software platform and add in mechanistic pharmacokinetic data on both Fischer 344 and Sprague Dawley rats that uncovered pharmacokinetic differences in the two strain of rats as well as the need for a more refined model description of the mixed lipid pool (MLP) handling into the hepato-lipid recirculation.

6.1.10 Point of Departure (POD) for Human Health Risk Assessment

The development of a POD for this assessment is focused on the results from the two-generation study (WIL Research Laboratories, Inc. 2001), which provided the most relevant NOAEC (300 ppm; LOAEC = 500 ppm). The results from the chronic toxicity / carcinogenicity study (Batelle 2004; Jean and Plotzke 2017) suggest a lower NOAEC (150 ppm) due only to the spacing of dosing compared to the reproductive studies (10, 30, 150, 700 ppm spacing in Batelle study versus 70, 300, 500, 700 ppm spacing in WIL; Gentry et al. 2017). Although questions remain about the relevancy of the reproductive effects to humans, use of the results from the two-generation study provides a conservative approach. A Benchmark Dose Level (BMDL) approach was used in the derivation of the POD.

6.1.10.1 Use of BMDL vs NOAEL

In general, a POD is either the externally derived NOAEL/C or the BMDL with uncertainty or safety factors applied to develop permissible exposure levels, or levels at which no relevant human risk is anticipated (USEPA 2012). In prior risk assessments conducted for D4, NOAELs

were used as the PODs (EC/HC 2008; SCCS 2010). Limitations to the NOAEL approach have been summarized in the 2012 USEPA Benchmark Dose Technical Guidance (USEPA 2012).

The best available science for identifying a POD is the BMDL approach (i.e. the maximum likelihood estimate of the dose associated with a specified increase in risk or change in response) and has several advantages over the NOAEL/C approach (Gentry et al. 2017). Therefore, considering the limitations of the NOAEL/LOAEL approach for determining the POD, the BMDL approach was chosen as the method for derivation of a POD for D4 in this assessment.

6.1.10.2 Dose-Response Assessment

In conducting the dose-response modeling, Gentry et al. (2017) considered three dose metrics. The first was the external animal inhalation exposure concentration. The second was the external exposure concentrations adjusted to continuous inhalation exposure from 6 h per day for 7 days per week in the two-generation study (Franzen et al. 2017). The third was the PBPK-derived internal dose metric (AUCs) for each exposure concentration. The parent compound was assumed to be the relevant toxic moiety and the AUC of the free D4 in the blood was considered to be the relevant dose metric for use in benchmark dose (BMD)- response modeling. The use of an internal dose metric (human equivalent concentration, HEC) to conduct the dose-response modeling is considered to be the best available science and the most relevant dose metric for D4 (Gentry et al. 2017; USEPA 2006; WHO 2010).

The AUC provides a more consistent and stable dose metric than the peak concentration when exposure is chronic. While alternative dose-metrics could be considered, such as Cmax, use of Cmax as the dose metric is very sensitive to changes in exposure, requiring more specific information regarding exposure patterns, which are usually lacking in the D4 animal studies and for exposure in humans. In addition, the use of the AUC, in general, results in more conservative estimates of acceptable intake and therefore will be used for this assessment. Consistent with the application of other PBPK models (Clewell and Andersen 1985; Clewell and Clewell 2008; Clewell et al. 2001a,b; Gentry et al. 2011; Reddy et al. 2008), it was assumed that the resulting AUC in the rat is the HEC (Gentry et al. 2017). The human PBPK model was

then used to estimate the AUCs for each of the exposure scenarios considered for comparison to the estimated POD, which is the result of the dose-response modeling.

The endpoint chosen as the most sensitive was the live litter size in the F1 generation of the two-generation rat reproduction study (WIL Research Laboratories, Inc 2001). The model chosen as the "best fit" for the endpoint was the linear continuous model with a constant variance over the dose groups.

Gentry et al. (2017) ran simulations with the rodent PBPK model using the female rat parameters to simulate exposure for 6 h per day, 7 days per week, for 70 days to 70, 300, 500 or 700 ppm D4 to derive the AUCs of the free D4 in the blood in the rat for each experimental concentration. Using the continuous animal exposure doses in the evaluation of the reproductive data, the estimated BMDL (or POD) was approximately 125 ppm. Using the internal dose-metrics (AUC of free D4 in the blood), the BMDL is approximately 30 mg-hrs/L blood/day. It was assumed that the resulting AUC in the rat is the HEC.

6.1.11 Discussion of the POD

The POD for the D4 human health risk assessment is 30 mg-hrs/L blood/day. This is a continuous exposure value and relevant to the general population human health risk assessment. This value also is used for consumer and worker exposure; however, it is conservative because the maximum duration of worker exposure is typically 8 hours or less a day, 5 days per week and consumer exposure is expected to be intermittent.

Much conservatism is built into the POD. As discussed in the ADME section, inhalation dose levels above 300 ppm result in saturation of metabolic capabilities in rats and as discussed by Pauluhn (2019) a mixed aerosol vapor exposure may be occurring above 300 ppm. Therefore, effects at dose levels above this level, 500 and 700 ppm, where effects were reported in the toxicological database for D4, are not appropriate for the derivation of human risk. Using this dose level, at which the saturation of metabolic capabilities occurred and where with rodent specific stress responses and/or tissue specific nonlinear doses may have occurred leading to nonspecific toxicity, provides a conservative endpoint for human health hazard assessment.

Additionally, the reproductive effects in rodents are not biologically relevant to humans (Dekant et al. 2017a,b). As summarized by Dekant et al. (2017a,b), there are physiological differences in the responses to D4 between rodents and humans. For example, there are no endometrial lesions in women that are analogous to the endometrial adenoma observed in the rat (Dekant et al. 2017a). Additionally, rat adenomas have little to no stromal proliferation, whereas polyps in women have well developed stroma (Dekant et al. 2017a). Carcinomas can also develop in human endometrial polyps whereas in rats, the endometrial adenomas are not pre-malignant (Dekant et al. 2017a). Therefore, basing the human health risk assessment on high dose level effects that are not biologically relevant to humans provides a conservative POD for human health risk assessment.

6.1.11.1 Application of Uncertainty Factors for Human Health Risk Assessment

When data from animal studies are extrapolated to humans to provide estimates of lifetime cancer risks or non-cancer hazard, potential differences in pharmacokinetics (metabolism) and pharmacodynamics (sensitivity) between the animal species and humans should be considered in the estimation of HECs (USEPA 2014; WHO 2005). This can be done by applying adjustments to the external exposure concentrations, or when data are available, deriving an internal dose metric associated with the target tissue dose. Because data on D4 are available in both human and animals, and application of human specific parameters are included in D4 PBPK modeling, the uncertainty factors typically applied to an animal derived NOAEL/NOAEC are not necessary. Therefore, based on the available data, the animal to human pharmacokinetic and pharmacodynamics uncertainty factor can be reduced for 10X to 1X. In addition, based on the human specific information in the PBPK models, it is also possible to reduce the intraspecies (between humans) uncertainty factor. The current PBPK model (McMullin et al. 2016) is not designed to estimate internal dose metrics for children. Therefore, child scenarios were qualitatively related to the PBPK results from adult scenarios evaluated in the PBPK analysis by Gentry et al (2017). This is an area of uncertainty in the POD and results of the PBPK modeling, and the uncertainty is addressed through an additional uncertainty factor (10X) discussed below. Furthermore, the resultant Margin of Exposures (MOEs) are very large and therefore protective of any potential exposures to children.

A benchmark MOE of 100 was considered the best available science based on a 10X uncertainty factor for intra-human variability, 1X uncertainty factor for extrapolation from animal-to-human (based on the use of PBPK data), and 10X uncertainty factor for remaining sources of uncertainty related to the database. This latter 10X uncertainty factor accounts for the current PBPK model (McMullin et. al., 2016) which is not designed to estimate internal dose metrics for children or pregnant/lactating women. This contrasts with the benchmark MOE of 1000 used by Gentry et al. (2017), which included an uncertainty factor of 10X for intra-human variability, 1X uncertainty factor for extrapolation from animal-to-human allowing for uncertainties in pharmacodynamics across species (it is expected that women would be less sensitive than the rodent to modifications in hormone balance), 10X uncertainty factor for the use of tumor rather than precursor data, and 3X uncertainty factor for remaining sources of uncertainty related to the database (lack of a chronic inhalation toxicity/carcinogenicity study in multiple species).

6.1.11.2 Evaluation of Alternative PODs

6.1.11.2.1 Respiratory Irritation

A LOAEC of 35 ppm (420 mg/m^3) based on alveolar macrophage foci and chronic interstitial inflammation of lung was reported in a 28-day study with rats exposed by nose only inhalation for 6 hours per day (Burns-Naas et al., 2002). This study is a supporting study, and not the key study for the evaluation of repeated-dose inhalation toxicity (not included in Table 6-4). The irritant and other effects reported in the study were not reported in any other subacute, subchronic, or chronic study. These effects were considered to be a generalized, non-specific adaptive response to a mild irritant, possibly exacerbated by aerosol exposure and extremely low humidity and not to be a specific effect of D4 (Pauluhn 2019). The changes noted in the lung after subchronic inhalation exposure to D4 were considered to be an adaptive response to a mild, non-specific irritant (Gentry et al. 2017). In support of this conclusion, no significant adverse changes in the respiratory tract were noted in other whole-body inhalation exposure studies in rats including the key study, the two-year chronic whole-body vapor inhalation study (Franzen et al. 2017; Dekant et al. 2017a). Although nose-only exposure is a guideline compliant route of entry, whole body exposure is more relevant to the assessment of human health effects. Therefore, the irritant effect by nose-only exposure in rats does not provide the most appropriate POD for human exposure to D4. In addition, the recent review by Pauluhn

(2019) has raised concerns about considering any respiratory tract effects following high dose inhalation exposure to D4 being considered even a classic mild irritant. Unlike the vapor phase, the liquid aerosol phase of D4 can readily be "emulsified" within the amphiphilic layer of pulmonary surfactant lining the alveolar lumen. While the pulmonary tissues are rapidly saturated with the vapor, the liquid phase is deposited with a markedly higher retention of mass. Ensuing physicochemical disturbances of surfactant can be expected due to the physicochemical properties of liquid D4. Pauluhn concluded that "Collectively, weighing all evidence in an integrated manner, experimental evidence suggests that the pulmonary toxicity of D4 is linked to the liquid aerosol phase which interacts physicochemically with surfactant followed by stereotypical compensatory responses". Pauluhn also concluded "In summary, due to the lack of any consistent changes in lung and liver weights (males), true biologically significant D4-related adverse effects could not be established."

6.1.11.2.2 Selection of Lowest NOAEC, Not Considering Dose Spacing

The POD selected by SCCS (2010) was a NOAEC of 150 ppm (LOAEC = 700 ppm based on increased uterine weight, increased incidence of endometrial cell hyperplasia, and an increased incidence of endometrial adenomas). The selection of this dose level is based on the lowest NOAEC reported in the 2-year rat chronic toxicity and carcinogenicity study (Batelle 2004; Jean and Plotzke 2017) and did not take into consideration dose spacing between that study and the dose levels in the two-generation rat reproduction study (WIL Research Laboratories Inc 2001; Siddiqui et al. 2007). In the two-generation rat reproduction study, the LOAEC was 500 ppm and the NOAEL was 300 ppm. The highest NOAEC (300 ppm) and the lowest LOAEC (500 ppm) are the most appropriate for use in risk assessment. Selecting the lowest NOAEC is overly conservative, not biologically relevant, and is not appropriate for human health risk assessment.

6.1.11.2.3 PODs Based on Liver and Kidney Effects

PODs based on liver and/or kidney effects are not relevant to the human health risk assessment. Repeated administration to rats of D4 by oral administration caused increases in liver weights at 400 and 1600 mg/kg (Dow Corning Corporation 1990); however, histopathological indications of hepatocellular damage and changes in clinical chemistry indicative of liver toxicity were not present. The absence of pathologic and carcinogenic liver effects after long-term inhalation

exposure to D4 further supports the conclusion that the liver weight changes represent an adaptive response. The liver changes induced by D4, therefore, are not considered adverse changes but represent adaptive reversible changes and should not be used in human risk characterization (FDA 2007; EMA 2010; Hall et al. 2012; SCCS 2005).

Inhalation exposure of rats to D4 at 700 ppm increased the absolute and/or relative kidney weight and resulted in a significant increase in chronic nephropathy in both sexes of rats exposed for two years (Batelle 2004). Available evidence indicates that chronic nephropathy is a distinctive disease entity in rats that has no human counterpart based on clinical manifestation, disease progression, and influencing factors. Therefore, the kidney effects observed after chronic inhalation of D4 at the highest concentration of 700 ppm likely have no relevance for human risk characterization (Hard et al. 2013).

6.1.12 Summary of Human Health Hazard

The toxicological database for D4 is extensive and has been reviewed and assessed in the peer reviewed literature as well as by regulatory authorities. The hazards identified in the D4 toxicological database occur at high concentrations, which exceed the metabolic capacity of the test systems and are therefore conservative endpoints to use in the human health hazard assessment for D4. In addition, the key hazard identified in the toxicological database for D4, reproductive effects in rodents, occurs through a MoA not relevant to human health. Therefore, the use of the reproductive toxicity effects is also a conservative approach to human health risk assessment (Dekant et al. 2017 a,b). For D4, the best available science for assessing the POD for risk assessment is the use of BMD and PBPK modeling. The POD to assess the human health risk from exposure to D4 is 30 mg-hrs/L blood/day, based on continuous exposure. This POD is used for all three exposure populations: worker, consumer, and general population as well as all susceptible populations.

6.2 Ecological Hazards

Relevant information regarding the ecological hazard of D4 was found in the D4 CSR (2018), the UK EA's Environmental Risk Assessment D4 report (Brooke et al. 2009), and NICNAS

(2018). In addition, a literature search was conducted to capture information that has become available subsequent to the publication of these authoritative reviews (i.e., post 2008). Studies and literature that have not been evaluated by one of these authoritative publications were reviewed following the procedure described in Section 2 and the reviews are attached as Appendix D. The exception to this procedure was the evaluation of studies that had already been evaluated by Bridges and Solomon (2016) using a detailed and transparent scoring system; these were not evaluated again. The information reviewed includes ecotoxicology studies, studies on metabolism using ecological receptors, and review articles that discuss information useful for the ecological risk assessment of D4.

A discussion of the information on ecological hazard of D4 is presented below, followed by a tabular presentation of the information (Table 6-8). Table 6-8 contains a summary of the new information (published from 2008 to the present) as well as information published prior to 2008. Appendix D contains the full reviews for the new information or any information that was not previously evaluated by an authoritative or peer-reviewed source. Table 6-8 includes the evaluation scores and the source of the score is noted if not done in this review process. The scores from the different sources were considered together to arrive at a conclusion of “high”, “medium” or “low” for the utility of the study in the ecological hazard evaluation (refer to Section 2). Review articles were not scored, as they largely relied on underlying information that was previously scored. This was also the case for published ecological risk assessment articles.

Following Table 6-8, a summary is provided which considers the overall reliability and relevance of the information and synthesizes it to provide a conclusion regarding the potential ecological hazard of D4.

A total of 25 studies were reviewed for the ecological hazard assessment. Twelve (12) studies or articles that have become available since 2008 contained information on the toxicological effects of D4 on ecological receptors, metabolism of D4 in ecological receptors, ecological risk assessments, or review articles relevant to the ecological risk assessment of D4. The remaining studies included had been published prior to 2008 or as part of other reviews. Where detailed reviews of these older studies had been previously conducted by an authoritative source or peer-

reviewed publication, the findings of these reviews were relied upon. These studies encompass a range of exposure durations and model organisms used to quantify ecological toxicity. The following discussion is presented in the same order the studies are presented in Table 6-8.

6.2.1 Aquatic Organisms

Springborn Laboratories, Inc. (1990d) conducted a prolonged acute study with rainbow trout (*Onchorhyncus mykiss*) up to the functional solubility[12] (22 µg D4/L) using a sealed flow-through system and found the 96-hr LC50 (concentration of a test substance causing 50% lethality in a group of test organisms) to be greater than 22 µg/L and the 14-day LC50 to be 10 µg/L. Rainbow trout were exposed to D4 in a closed flow-through system for 18 days and evaluated acute and prolonged effects on survival as well as body residues of D4 (Dow Corning Corporation 1992). While only one test concentration was used, no effects on survival were observed after 4 days of exposure (96-hr LC50 >23 µg/L; 96-hr no-observed-effect concentration [NOEC] ≥23 µg/L; 4 cm trout). The study showed that smaller trout (4 cm) had higher mortality rates (80%) compared to larger trout (7 cm, 0% mortality) after 18 days of exposure to D4. The study also reported 18-day LC50 and NOEC values for the 4 cm and 7 cm trout. These reported values were LC50 <23 µg/L and a NOEC ≤23 µg/L for 4 cm trout and a LC50 >31 µg/L and a NOEC ≥31 µg/L for 7 cm trout (Dow 1992). A BCF of 5,000 – 15,000 L/kg was also calculated after 18 days for fish surviving until the test termination, although the exposure in this study may not represent steady state. Another study conducted by Dow Corning addressed acute (4-day) and prolonged exposure (14 days) of rainbow trout (*O. mykiss)* to radiolabeled D4 in an open continuous-flow system (Dow Corning Corporation 2008a). The study was conducted under GLP and followed OECD Guideline 204. The study reported the 14-day LC50 value as 17 µg/L and the NOEC as 6.8 µg/L. At four days of exposure, very little mortality occurred; thus, the 96-hr LC50 was greater than the highest test concentration, 29 µg/L. The CSR (2018) rated Springborn (1990d) and Dow (2008a) to be reliable without restriction, but rated Dow (1992) as reliable with restrictions. Bridges and Solomon (2016)

[12] The functional solubility is defined as the maximal achievable solubility of D4 under the specific conditions and dilution water quality for a particular study.

consider the quality of the Springborn (1990d) and Dow (2008a) to have no major weaknesses, but those authors did not evaluate Dow (1992).

Firmin et al. (1984) conducted acute exposures with multiple species. All tests were conducted in open, static systems (CSR 2018). LC50 values were >1,000 mg/L for multiple fish species (bluegill, *Lepomis macrochirus*; mummichog, *Fundulus heteroclitus;* rainbow trout, *O. mykiss*). Firmin et al. (1984) also determined a 96-hour EC50 >1,000 mg/L for the shrimp *Crangon crangon,* 24-hour EC50 >500 mg/L for brine shrimp *Artemia salina*, and a 14-day EC50 >2,000 mg/L for the blue-green alga (cyanaobacteria) *Anabaena flos-aquae.* (The EC50 is the concentration of test substance causing a specified effect (e.g., inhibition, immobility) in 50% of a group of test organisms). Although the CSR (2018) rated this study as reliable with restrictions, Brooke et al. (2009) concludes that results presented by Firmin et al. (1984) should not be considered valid for use in risk assessments because of uncertainties over the dissolved exposure concentrations used in these tests.

Two acute studies were conducted with aquatic invertebrates. The first study was an acute (48 hour test, sealed flow-through system) with the water flea, *Daphnia magna*, which found no toxicity (immobilization) at the functional solubility; thus, the EC50 (concentration causing an adverse effect to 50% of the test organisms) was >15 µg/L and the NOEC was ≥15 µg/L (Springborn 1990b). The second study was an acute sealed flow-through test with the mysid *Mysidopsis bahia*, a marine/estuarine organism, which resulted in a 96-hour LC50 >9.1 µg/L and a NOEC (survival) of ≥9.1 µg/L, the functional solubility (Springborn 1990f). The CSR (2018) rated these studies to be reliable without restriction. Bridges and Solomon (2016) considers the quality of these two studies to have no major weaknesses but reduced the relevance score to reflect that these were not prolonged exposures and dose-response data were not observed.

One acute study (sealed, static system) was conducted with green algae, *Selenastrum capricornutum,* which resulted in a 96-hour EC50 >22 µg/L and a NOEC (cell density) of ≥22 µg/L, the functional solubility (Springborn 1990a). The CSR (2018) rated this acute algal study to be reliable without restriction and Bridges and Solomon (2016) considers the quality of this study to have no major weaknesses.

Four prolonged acute toxicity tests were conducted with fish; three of which are discussed above (Springborn 1990d; Dow 1992, 2008a). The fourth prolonged acute study was conducted with the estuarine/marine fish, sheepshead minnow (*Cyprinodon variegatus)* in a sealed flow-through system, which resulted in a 14-day LC50 of >6.3 µg/L and a NOEC (survival) of ≥6.3 µg/L, the functional solubility (Springborn 1990e). The CSR (2018) rated Springborn (1990d); Dow (2008a); and Springborn (1990e) studies to be reliable without restriction, but rated Dow (1992) as reliable but with restrictions. Bridges and Solomon (2016) considers the quality of the Springborn (1990d), Dow (2008a), and Springborn (1990e) studies to have no major weaknesses, but those authors did not evaluate Dow (1992). Because only one exposure concentration was used in Dow (1992), the score was slightly reduced.

Two studies were available that assessed the chronic effects of D4 in fish. The first study was a 28-day bioconcentration study conducted by Springborn with fathead minnow (*Pimephales promelas*) under sealed flow-through conditions (Springborn 1991e). While this study did not aim to collect toxicity data, it did report that no mortality occurred at the measured test concentration of 0.26 µg/L (NOEC ≥0.26 µg/L). Given that the objective of this bioconcentration study was not to determine the level at which toxicity would occur, a number of criteria were not met and thus this study was given a relatively poor score of 58 for toxicity (Table 6-8). The CSR (2018) and Bridges and Solomon (2016) did not review this fathead minnow bioconcentration study. The second available chronic study was an early life stage exposure (sealed system with a modified constant flow serial diluter) with rainbow trout *O. mykiss*, which provided a NOEC for survival and growth of ≥ 4.4 µg/L (Springborn 1991c), the highest test concentration; this report was considered by Bridges and Solomon (2016) to have no major weaknesses in quality and the CSR (2018) concluded that this study was reliable without restriction.

One chronic study was available for aquatic invertebrates using *D. magna*. *D. magna* were exposed to aqueous concentrations of D4 for 21 days in a sealed flow-through system with no headspace (Springborn 1990c). Survival was reduced at the highest test concentration, which was 15 µg/L (considered the 21-day lowest-observed-effect concentration [LOEC]); the 21-day LC50 was >15 µg/L and the 21-day NOEC for survival was reported as 7.9 µg/L. Reproduction

was unaffected by any of the tested concentrations (21-day NOEC for reproduction ≥ 15 µg/L). The CSR (2018) and Bridges and Solomon (2016) found this study to be reliable without restriction. A re-evaluation of this study (Smithers Viscient 2018) indicates that the results of this study should be based on the classic chronic daphnid endpoints of reproduction and growth, and the initially reported NOEC value for survival of 7.9 µg/L should not be used. The overall survival rate of 77% in the high dose group is the arithmetic mean of just two replicates, where the survival rate was below 80% for only one replicate (replicate 1: 67%; replicate 2: 87%). Also, Fairbrother and Woodburn (2016) note that the mean effect concentration on *Daphnia* survival (77%) was only slightly below the allowable 80% survival rate for controls. In this study, no adverse effects on reproduction or growth were observed. The reproduction and growth of neonates is the population-relevant endpoint and should take precedence in the scientific evaluation of the study and assignment of a NOEC. Although the mortality 21-d NOEC had been determined as 7.9 µg/l, there is a lot of uncertainty associated with this NOEC due to differences in the two replicates and the fact that the overall survival rate of 77% is only slightly below the allowable rate. Moreover, the reproduction and growth of neonates is the population-relevant endpoint. Therefore the 21-d NOEC for growth and reproduction of ≥15 µg/L was taken as a key value for the chronic invertebrate toxicity endpoint.

6.2.2 Sediment Organisms

Kent et al. 1994 reported on toxicity tests conducted with sediment-dwelling invertebrates. Kent et al. 1994 is the peer-reviewed publication for two internal reports, Springborn (1991a,b). Springborn (1991a) used a sealed flow-through system for the water and sediment tests. A 14-day test with aqueous exposure with the midge *Chironomus tentans* resulted in a NOEC (survival, growth) of ≥15 µg/L and an LC50 >15 µg/L (Springborn 1991a). A 14-day test with sediment exposure using three levels of organic carbon (low, medium and high) resulted in a LC50 >130 mg/kg for low organic carbon sediment and equal to 170 mg/kg for medium organic carbon (Springborn 1991a). The 14-day NOEC values were 65 mg/kg for growth and ≥130 mg/kg for mortality in the low organic carbon content sediment, and 120 mg/kg for both growth and mortality in the medium organic carbon content sediment. This study (Springborn 1991a) was reviewed in the CSR (2018) and found to be reliable without restriction. In addition, Bridges and Solomon (2016) consider the quality of Springborn (1991a) to have no major

weaknesses. However, Springborn repeated the portion of the study conducted with high organic carbon sediment (Springborn 1991b), as they had observed an inconsistent growth response in that sediment in the first study. Using an open flow-through system, the NOEC for survival and growth in the high organic carbon sediment was 54 mg/kg and the LC50 was >170 mg/kg in this second study. This study (Springborn 1991b) was reviewed in the CSR (2018) and found to be reliable without restriction. In addition, Bridges and Solomon (2016) consider the quality of Springborn (1991b) to have no major weaknesses.

Three studies reported during or since 2008 have addressed D4 toxicity to sediment-dwelling invertebrates. In an OECD 218 study with the harlequin fly (*Chironomus riparius*), artificial sediment was spiked with D4 and the overlying water was not renewed. The test chamber was closed with a loose, plastic cover with a glass pipette inserted into each chamber for aeration (Wildlife International, Ltd. 2008a). The reported endpoints were: 28-day LC50 = 114 mg/kg, NOEC = 44 mg/kg, and LOEC = 131 mg/kg, with the NOEC / LOEC based on survival and emergence ratio (Wildlife International, Ltd. 2008a). Two studies (both using methods the same or similar to OECD 225) tested effects in California blackworm (*Lumbriculus variegatus*). Wildlife International, Ltd. used an open artificial sediment and semi-static water system with this organism and reported the following endpoints: 28-day EC50 = 9.32 mg/kg, NOEC <0.73 mg/kg, and LOEC = 0.73 mg/kg, with the NOEC, LOEC and EC50 based on survival and reproduction (Wildlife International, Ltd. 2009). Springborn spiked a natural sediment in a closed static sediment-water system and determined a 28-day EC50 >32 mg/kg, NOEC = 13 mg/kg, and LOEC = 19 mg/kg (Springborn 2009). The NOEC and LOEC are based on survival and reproduction, with the EC50 additionally based on biomass. As discussed in Nusz et al. (2018) and Bridges and Solomon (2016), the use of artificial sediment, with peat as the only source of organic matter, was a major weakness in this study. Therefore, the study conducted with natural sediment (Springborn 2009) provides the preferred endpoint for toxicity to *Lumbriculus variegatus.* All three studies (Springborn 2009; Wildlife International, Ltd. 2008a, 2009) were considered reliable without restriction in the CSR (2018).

6.2.3 Other Information

Two papers available since 2008 discuss the metabolism of D4 in ecological receptors. A report (Wildlife International, Ltd. 2008b) describes oral administration of rainbow trout with a single dose of 15 mg D4/kg fish in which 82% of the dose was absorbed and 69% of the radioactivity was found in the fish carcass. Most of the radioactivity was measured in the bile, and 40% in liver was attributed to metabolites, while 18% of the recovered dose was eliminated in the feces and identified as the parent compound. Data from the Wildlife International, Ltd. (2008b) study were also presented in a peer-reviewed publication by Domoradzki et al. (2017a), who reported on the metabolism of D4 in rainbow trout. The authors used mean residue data to obtain an estimated metabolism rate constant of 0.10 day^{-1} for D4; using first-order kinetics, this results in a fish metabolism half-life for D4 of approximately 6.7 days and an overall D4 dissipation half-life (metabolism + loss due to elimination/storage) in trout of approximately 1.2 days. Metabolic studies of D4 with rainbow trout (Cantu and Gobas 2019) and benthic invertebrate species (Selck et al. 2019) found the compounds to be highly metabolizable, with metabolism rate constants (k_M) that influence bioaccumulation. These findings are useful in bioaccumulation/biomagnification models that may not account for metabolism.

Review articles and weight of evidence articles were also assessed. Bridges and Solomon (2016) published a QWoE analysis using available data on the properties of D4, D5 and D6 as related to persistence, bioaccumulation, toxicity and long-range transport. The Supplemental Information (SI) for Bridges and Solomon (2016) contains detailed reviews of each study with assigned scores for quality and relevance. The authors concluded that cVMSs should not be classified as persistent, and studies in food webs and toxicokinetics information support the finding that cVMS do not biomagnify and that concentrations measured in robust studies in the environment are below toxicity thresholds. The study also concluded that traditional measurements used for persistence and biomagnification may not be suitable for cVMSs. Fairbrother and Woodburn (2016) reviewed existing aquatic toxicity data for D4. They concluded that artificially closed systems are not appropriate testing methods due to increased sensitivity. Narcosis MoA and chemical “activity” (fugacity) explain the lack of toxicity caused by D4 to aquatic organisms when exposure occurs in environmentally realistic conditions. Kent et al. (1994) also concludes that D4 environmental toxicity is due to the narcosis mode of action.

Nusz et al. (2018) cited Kent et al. (1994) as demonstrating that D4 is not expected to biomagnify in the aquatic food chain. Peter Fisk Associates (2010) captures the contents of the UK EA's 2009 report (Brooke et al. 2009). The purpose of the document is to set out an approach to evaluating the environmental effects properties of D4 suitable for REACH registration, building on the UK EA's assessment. The only notable comment by these authors echoes previous comments on the reliability of the study with *Lumbriculus variegatus* with artificial sediment (Wildlife International, Ltd. 2009). Wang et al. (2013a) is a review article from researchers with Environment Canada discussing ecotoxicity, toxicology, detection, occurrence, and fate of cVMSs. The article provides recommended physico-chemical properties and the most sensitive ecotoxicity values. The Wang et al. (2013a) review suggests that there is no evidence of trophic magnification of D4 in aquatic food webs, though bioconcentration and bioaccumulation may be possible. High concentrations of cVMS in indoor air and biosolids resulted from point sources. Concentrations of cVMS detected in water, sediment, and soil were all below their NOECs. Buser (2015) is a corrigendum to Wang et al. (2013a) and does not present any new data.

Several published ecological risk assessments were also reviewed. Hobson and Silberhorn (1995) conducted an ecological risk assessment for D4. The effects assessment was based on the results of industry-sponsored aquatic toxicity studies conducted on fish and invertebrates; these are the same studies described previously. Toxicity from aqueous exposure was characterized as requiring extended, continuous exposure and being limited to narcosis-like effects on behavior and survival. The exposure assessment was based on physico-chemical and environmental fate properties, modeling, and monitoring data from four sewage treatment plants. The authors concluded that the concentrations of D4 in aquatic ecosystems are expected to be low and transient in water and sediments. Comparison of predicted surface water concentrations with the lowest NOEC from toxicity studies indicated conservative 64-to 444-fold margins of safety (MOSs) for organisms exposed to the water column and 157- to 1,080-fold MOS for benthic organisms. Rapid volatilization and additional dilution in most aquatic environments would increase this margin of safety for aquatic life even further. Redman et al. (2012) presents a risk assessment using previously published data. This paper compares measured tissue concentrations of cVMS (including D4) in fish and benthic invertebrates with critical target lipid

body burdens (CTLBBs), as estimated with the target lipid model (TLM), to evaluate risk. The analysis included the contribution from metabolites to the overall tissue residues using a food chain model calibrated to laboratory and field data. The findings suggest that there is little evidence for risk of adverse effects related to cVMS under present-day emission levels. This model, which resulted in an HC_5 [hazardous concentration to only the most sensitive 5% of species in a species sensitivity distribution] CTLBB of 2.6 µg/mol lipid, was used in the ecological risk evaluation by Nusz et al. (2018), which in turn forms the basis of the ecological risk assessment for D4 conducted therein. The 2.6 µg/mol lipid value was used as a threshold for estimating D4 levels in tissue that can cause toxicity in aquatic receptors (Nusz et al. 2018).

Woodburn et al. (2018) compared field sediment concentrations (from locations worldwide) of cVMS to chronic NOECs from benthic lab studies. For D4, there were five benthic lab studies considered suitable (data from the *L. variegatus* study by Wildlife International, Ltd. 2009 were excluded). A fugacity approach was used and risks evaluated by both deterministic hazard quotient (HQ) and probabilistic methods. The lack of overlap between the sediment concentration data (expressed as 95% cumulative distribution function, CDF) compared to benthic invertebrate NOEC values using either the deterministic or probabilistic method led to a conclusion of no risk. The Woodburn et al. (2018) article was also summarized by Nusz et al. (2018), who mention that the highest sediment concentrations of D4 were found near urban waterways and near wastewater treatment plants (WWTPs) and that overall, the 95th percentile of measured D4 concentrations in sediment did not overlap with benthic invertebrate toxicity thresholds (Nusz et al. 2018).

Table 6-8. Ecological effects and related information

Method	Response	Results[1]	Remarks	Evaluation (score based on review)[2]	Klimisch score (from CSR Report)[3]	Reference	Reference ID
Toxicity - 96 hour and 14 day exposure of rainbow trout (*Oncorhnchus mykiss*) in flow-through, sealed system, no headspace	Mortality	The functional solubility was 22 µg/L.[4] 96-hour LC50 >22 µg/L 96-hour NOEC ≥22 µg/L 14-day LC50 = 10 µg/L 14-day LOEC = 6.9 µg/L 14-day NOEC = 4.4 µg/L NOEC / LOEC based on survival	Followed TSCA guideline EPA OTS 797.1400 with rainbow trout. Used GC-MS for analysis. Measured treatments were 2.9, 4.4, 6.9, 12 and 22 µg D4/L.	Reviewed by CSR18A and Bridges and Solomon (BRIDG16A). Bridges Score = 3.6 for methods, and 3.8 for adverse effect relevance (14-day results).	1	Springborn Laboratories, Inc. 1990d (Study director: J.V. Sousa)	SPRIN90D
Toxicity - 96 hour and 18 day exposure of rainbow trout (*Oncorhnchus mykiss*) in closed flow-through system with headspace; tested response of two sizes of fish at saturation level	Mortality, bioconcen-tration factor (BCF)	The functional solubilities were not specifically reported. The highest test concentrations in each experiment was 23 µg/L for 4 cm (apr. 1 g) fish and 31 µg/L for 7 cm (apr. 5 g) fish and were at the saturation levels; thus, assumed to be the functional solubilities. 96-hr LC50 >23 µg/L for 4 cm (apr. 1 g) fish 96-hr NOEC ≥23 µg/L for 4 cm (apr. 1 g) fish 18-day LC50 < 23 µg/L for 4 cm (apr. 1 g) fish, >31 µg/L for 7 cm (apr. 5 g) fish 18-day NOEC < 23 µg/L (4 cm, ~1 g fish); ≥31 µg/L (7 cm, ~5g fish) At 23 µg/L, 80% of 4 cm fish died NOEC based on survival BCF of 5,000 – 15,000 L/kg though may not be representative of steady state conditions.	Guideline study conducted under GLP study. However, only one test concentration was used for each size fish groups.	61; Reviewed by CSR18A	2	Dow Corning Corporation 1992 (Study director: R.B. Annelin)	DOWCO92A

Method	Response	Results[1]	Remarks	Evaluation (score based on review)[2]	Klimisch score (from CSR Report)[3]	Reference	Reference ID
Toxicity - OECD 204 (Fish, 96 hour and 14 day toxicity test) with *Oncorhynchus mykiss*, in a flow-through, open system	Mortality	The functional solubility was not specifically reported. The highest test concentration in the study was 29 µg/L and assumed to be the functional solubility. 96-hr LC50 >29 µg/L 96-hr LC05 = 29 µg/L 14-day LC50 = 17 µg/L 14-day NOEC = 6.8 µg/L 14-day LOEC = 13 µg/L NOEC, LOEC based on mortality	Guideline study conducted under GLP with well-documented findings. 14-day exposure to radiolabeled D4 in continuous flow system, open system. Measured treatments were 1.9, 3.4, 6.8, 13 and 29 µg D4/L.	32; Reviewed by CSR18A and Bridges and Solomon (BRIDG16A). Bridges Score = 3.7 for methods and 4 for effects relevance (2 effects).	1	Dow Corning Corporation 2008a (Study director: K.R. Drottar	DOWCO08A
Toxicity - 96 hour exposure with *Lepomis macrochirus, Oncorhynchus. mykiss, Crangon crangon, and Fundulus heteroclitus;* 24 hour exposure with *Artemia salina;* 14 day exposure with algae *(Anabaena flos-aquae)*, All conducted in static, open system	Mortality	96 h LC50 >1000 mg/L for *Lepomis macrochirus* 96 h LC50 >1000 mg/L for *O. mykiss* 96 h EC50 >1000 mg/L for *Crangon crangon* 96 h LC50 >500 mg/L and >1000 mg/L for *Fundulus heteroclitus* 24 h EC50 >500 mg/L with *Artemia salina* 14-day EC50 for *Anabaena flos-aquae* >2000 mg/L	The UK EA (EA09A) summarizes these experiments as being performed at concentrations greater than the water solubility of D4, and in open static systems which volatilization loss would occur.	Reviewed by CSR18A and EA09A	2	Firmin et al. 1984	FIRMI84A
Toxicity - 48 hour exposure with *Daphnia magna*, flow-through, sealed system, no headspace	Immobiliza-tion	The functional solubility was 15 µg/L. 48-hour EC50 >15 µg/L 48-hour NOEC ≥15 µg/L EC50, NOEC based on immobilization	Followed TSCA guideline EPA OTS 797.1300. Analysis was by GCMS using a purge and trap injector. Measured treatments at 0, 24, and 48 h were 15, 7.8, 3.7, 2.9 and 1.7 µg D4/L. No mortality was observed.	Reviewed by CSR18A and Bridges and Solomon (BRIDG16A). Bridges Score = 3.7 for methods and 1.6 for effect relevance.	1	Springborn Laboratories, Inc. 1990b (Study director: P.C. McNamara)	SPRIN90B

Method	Response	Results[1]	Remarks	Evaluation (score based on review)[2]	Klimisch score (from CSR Report)[3]	Reference	Reference ID
Toxicity - 96 hour exposure with *Mysidopsis bahia*, flow-through, sealed system, no headspace	Mortality	The functional solubility was 9.1 µg/L. 96-hour LC50 >9.1 µg/L 96-hour NOEC ≥9.1 µg/L NOEC based on survival	Followed TSCA EPA OTS 797.1930. Measured treatments were 9.1, 6.9, 6, 3.7, 2.2, 1.6 µg D4/L. No mortality was observed.	Reviewed by CSR18A and Bridges and Solomon (BRIDG16A). Bridges Score = 3.7 for methods and 1.6 for effect relevance.	1	Springborn Laboratories, Inc. 1990f (Study director: D.C. Surprenant)	SPRIN90F
Toxicity - 96 hour toxicity text for algae, *Selenastrum capricornutum*, static, sealed system, no headspace; limit test	Cell density	The functional solubility was 22 µg/L. 96-hour EC50 >22 µg/L initial 96-hour NOEC ≥22 µg/L initial NOEC based on cell density	Followed TSCA guideline EPA OTS 797.1050. Used GC-MS for analysis. Measured concentration for exposure was variable; concentration was 3.3 µg D4/L by end of exposure. No effects were observed.	Reviewed by CSR18A and Bridges and Solomon (BRIDG16A). Bridges Score = 3.1 for methods, and 3.2 and 2.2 for adverse effect relevance (two effects).	1	Springborn Laboratories, Inc. 1990a (Study director: J.M. Giddings)	SPRIN90A
Toxicity - 14 day exposure with *Cyprinodon variegatus*, flow-through, sealed system, no headspace	Mortality	The functional solubility was 6.3 µg/L. 14-day LC50 >6.3 µg/L 14-day NOEC ≥6.3 µg/L NOEC based on survival	Followed TSCA EPA OTS 797.1400. Measured treatments were 6.3, 4.2, 2.3, 1.6, and 1.3 µg D4/L. No mortality was observed.	Reviewed by CSR18A and Bridges and Solomon (BRIDG16A). Bridges Score = 3.7 for methods and 2.4 for effect relevance.	1	Springborn Laboratories, Inc. 1990e (Study director: J.V. Sousa)	SPRIN90E
Toxicity - 28 day exposure with *Pimephales promelas*, flow-through, sealed system, no headspace, bioconcentration study	Mortality	The functional solubility was not reported. This study did not use the saturation system; it used radiolabeled D4 at a very low concentration (nominal concentration was 0.5 µg/L). 28-day NOEC ≥0.26 µg/L, based on survival	Followed TSCA EPA OTS 797.1520. Treatments was 0.26 µg D4/L. No mortality was observed.	58 (this score is based on toxicity determination, not biocon-centration determination)	N/A	Springborn Laboratories, Inc. 1991e (Study director: P.H. Fackler)	SPRIN91E

Method	Response	Results[1]	Remarks	Evaluation (score based on review)[2]	Klimisch score (from CSR Report)[3]	Reference	Reference ID
Toxicity - Early life stage exposure with *Oncorhynchus mykiss*, sealed system with a modified constant flow serial diluter, no headspace	Embryo hatching success, percent normal larvae at hatching, larval survival, larval growth (measured by total length and dry weight)	The functional solubility was 20–30 µg/L. 93-day NOEC ≥≥4.4 µg/L, based on survival and growth	Followed TSCA EPA OTS 797.1600. Measured treatments were 0.25, 0.53, 1.1, 1.9 and 4.4 µg D4/L. No effects were observed.	Reviewed by CSR18A and Bridges and Solomon (BRIDG16A). Bridges Score = 3.9 for methods and 2.4 for adverse effect relevance (4 effects with same score)	1	Springborn Laboratories, Inc. 1991c (Study director: J.V. Sousa)	SPRIN91C
Toxicity - 21 day exposure with *Daphnia magna*, flow-through, sealed system, no headspace	Mortality, reproduction, growth	The functional solubility was 26 µg/L. 21-day LC50 >15 µg/L 21-day NOEC ≥15 µg/L (reproduction and growth) Survival in high dose group was 87% in one replicate and 67% in the other but upon re-analysis, a NOEC based on survival was not considered to be the relevant endpoint.	Followed TSCA guideline EPA OTS 797.1330 (Daphnid Chronic Toxicity Test). Analysis was by GCMS using a purge and trap injector. Measured treatments were 15, 7.9, 4.2, 1.8 and 1.7 µg D4/L.	Reviewed by CSR18A and Bridges and Solomon (BRIDG16A). Bridges Score = 3.7 for methods and 3.2 (survival), 2.4 (reproduction) for effect relevance.	1	Springborn Laboratories, Inc. 1990c (Study director: P.C. McNamara) Study re-evaluation: Smithers Viscient 2018	SPRIN90C
Toxicity - 14 day aqueous exposure with *Chironomus tentans*; 14 day sediment exposure with *Chironomus tentans*	Mortality, larval growth	Peer reviewed version of SPRIN91A and SPRIN91B. Please see details below.		N/A	N/A	Kent et al. 1994	KENT94A

Method	Response	Results[1]	Remarks	Evaluation (score based on review)[2]	Klimisch score (from CSR Report)[3]	Reference	Reference ID
Toxicity - 14 day aqueous exposure with *Chironomus tentans*, flow-through, sealed system; 14 day sediment exposure with *Chironomus tentans*, flow-through, sealed system	Mortality, growth	Aqueous: 14-day NOEC ≥15 µg D4/L (survival, growth), 14-day LC50 >15 µg/L. The functional solubility was 15 µg/L. Low Organic Carbon Sediment: 14-day LC50 >130 mg/kg 14-day LOEC (growth) = 130 mg/kg 14-day NOEC (growth) = 65 mg/kg 14-day NOEC (mortality) ≥130 mg/kg Medium Organic Carbon Sediment: 14-day LC50 = 170 mg/kg 14-day LOEC (mortality, growth) = 250 mg/kg 14-day NOEC (mortality, growth) = 120 mg/kg High Organic Carbon Sediment: Sediment exposures for high organic carbon study were repeated in SPRING91B due to inconsistencies in observed growth (see SPRING91B for sediment experiment)	GLP study. Aqueous treatments were 15, 6.5, 2.9, 1.2 and 0.49 µg D4/L. GC-MS used. Low organic carbon (0.27% TOC) treatments were 130, 65, 32, 17, and 6.8 mg D4/kg (measured) Medium organic carbon (2.3% TOC) treatments were 250, 120, 76, 36, and 18 mg D4/kg (measured) High organic carbon sediment exposures were repeated see SPRING91B. Peer-reviewed version is KENT94A.	Reviewed by CSR18A and Bridges and Solomon (BRIDG16A). Bridges Score = 3.4 for methods and a range of 1.4 – 2.4 for effect relevance (six effects)	1	Springborn Laboratories, Inc. 1991a (Study director: P.C. McNamara)	SPRIN91A
Toxicity - 14 day sediment exposure with *Chironomus tentans*, flow-through, open system	Mortality, growth	High Organic Carbon Sediment: 14-day NOEC = 54 mg/kg (survival, growth) 14-day LOEC = 170 mg/kg (survival, growth) 14-day LC50 >170 mg/kg	Used modified ASTM method (1987). High organic carbon (4.1% TOC) treatments were 170, 54, 19, 7.4, and 2.6 mg D4/kg (measured) Peer-reviewed version is KENT94A.	Reviewed by CSR18A and Bridges and Solomon (BRIDG16A). Bridges Score = 3.6 for methods, 1.4 for effect relevance for survival and growth	1	Springborn Laboratories, Inc. 1991b (Study director: P.C. McNamara)	SPRIN91B

Method	Response	Results[1]	Remarks	Evaluation (score based on review)[2]	Klimisch score (from CSR Report)[3]	Reference	Reference ID
Toxicity - OECD 218 (Sediment-water *Chironomus riparius* toxicity test using spiked sediment), closed system, test water not renewed during test, formulated sediment. The test chamber was closed with a loose, plastic cover with a glass pipette inserted into each chamber for aeration	Mortality, emergence ratio	28-day LC50 = 114 mg/kg with 95% confidence limits of 96 and 136 mg/kg 28-day NOEC = 44 mg/kg 28-day LOEC = 131 mg/kg NOEC and LOEC based on survival and emergence ratio	Guideline study conducted under GLP with well-documented findings. Used artificial sediment and no flow of overlying water. Source of organic carbon in sediment was peat. Measured treatment levels were 6.5, 7.9, 19, 44, 131, and 355 mg D4/kg. TOC = 4.1%	30; Reviewed by CSR18A and Bridges and Solomon (BRIDG16A). Bridges Score = 3.8 for methods, 2.4-3.6 for effect relevance (4 effects)	1	Wildlife International, Ltd. 2008a (Study authors: H.O. Krueger, S.T. Thomas, and T.Z. Kendall)	WILDL08A
Toxicity - OPPTS 850.1735/ASTM E1706-00/OECD 225 (Sediment-water *Lumbriculus variegatus* toxicity test using spiked sediment), open semi-static system, formulated sediment	Mortality, growth, reproduction	28-day EC50 = 9.32 mg/kg with 95% confidence limits of 4.38 and 25.4 mg/kg, based on survival and reproduction. 28-day NOEC <0.73 mg/kg 28-day LOEC 0.73 mg/kg NOEC and LOEC based on survival and reproduction. Survival and reproduction were more sensitive than growth.	Guideline study conducted under GLP with well-documented findings. Used artificial sediment and semi-static flow of overlying water. Source of organic carbon in sediment was peat. Measured treatment levels were 0.73, 1.5, 3.1, 5.8, 11, and 38 mg D4/kg. TOC = 2.4%	33; Reviewed by CSR18A and Bridges and Solomon (BRIDG16A). Bridges Score = 3.9 for methods (but lowered score based on artificial sediments), 0-3.8 for effect relevance (3 effects)	1	Wildlife International, Ltd. 2009 (Study authors: H.O. Krueger, S.T. Thomas, and T.Z. Kendall)	WILDL09A
Toxicity - OECD 225 (Sediment-water *Lumbriculus variegatus* toxicity test using spiked sediment), closed static system, natural sediment	Mortality, biomass, reproduction	28-day NOEC (survival, reproduction) = 13 mg/kg 28-day LOEC (survival, reproduction) = 19 mg/kg 28-day EC50 (survival, reproduction, biomass) >32 mg/kg Since no concentration tested resulted in ≥50% reduction in survival or biomass, the EC50 value was empirically estimated to be >32 mg/kg, the highest mean measured concentration tested.	OECD 225; Guideline study conducted under GLP with well-documented findings. Used natural sediment and no flow of overlying water. Measured treatments were 1.2, 3.2, 8.8, 13, 19 and 32 mg a.i./kg. TOC = 2.2%	29; Reviewed by CSR18A and Bridges and Solomon (BRIDG16A). Bridges Score = 3.9 for methods, 1.6-2.4 for effect relevance (2 effects)	1	Springborn Smithers Laboratories 2009 (Study director: C. Picard)	SPRIN09A

Method	Response	Results[1]	Remarks	Evaluation (score based on review)[2]	Klimisch score (from CSR Report)[3]	Reference	Reference ID
Metabolism - *In vivo* metabolism study: oral gavage, mature rainbow trout (*Oncorhynchus mykiss*)	D4 concentrations in biological samples to determine *in vivo* metabolism	79% of administered dose recovered. 82% of dose was absorbed. 69% of radioactivity found in the fish carcass. Out of total radioactivity measured, the 95% found in the bile and 40% found in the liver was attributed to metabolites. 18% of recovered dose was eliminated in the feces and was recovered as the parent compound. Urinary excretion is a minor elimination pathway.	Non-guideline / GLP study 15 mg/kg nominal dose Trial One: four mature rainbow trout. Concentrations of parent D4 and total radioactivity were determined for bile, blood, digestive tract, testes (with milt), fat, liver, carcass, urine, feces Trial Two: four mature rainbow trout. Evaluated D4 metabolites in urine. This study contains data that appear in the peer-reviewed publication, DORMOR17A.	34; Bridges and Solomon (BRIDG16A). Bridges Score = 3.86 for methods, 4.0 for effect relevance	N/A	Wildlife International, Ltd. 2008b (Study director: T.A. Springer)	WILDL08B
Metabolism - *In vivo* metabolism study: oral gavage, mature rainbow trout (*Oncorhynchus mykiss*)	D4 concentrations in biological samples to determine *in vivo* metabolism	Of the administered dose, 79% (D4) was recovered by the end of the study (96-h); a significant portion was eliminated in feces. Approx. 40% of the radioactivity in the liver was due to metabolites. Using mean residue data, the estimated metabolism rate constant was 0.10 day^{-1}. Assuming first-order kinetics, the metabolism half-life is approx. 6.7 days and the overall dissipation half-life (metabolism + loss due to elimination/storage) in trout was approximately 1.2 days. Clearance may occur via enterohepatic circulation of metabolic products in bile with excretion via the digestive tract and urinary clearance of polar metabolites.	Two D4 trials were conducted. This is the peer-reviewed publication version for data developed in WILDL08B.	33	N/A	Domoradzki et al. 2017a	DOMOR17B
Review / weight of evidence (WOE) - QWoE evaluation to characterize persistence, bioaccumulation, toxicity and long-range transport of cVMSs	N/A	CVMSs should not be classified as persistent. cVMSs do not biomagnify and that concentrations measured in robust studies in the environment are below toxicity thresholds. Traditional measurements used for persistence and biomagnification may not be suitable for cVMSs.	WOE analysis	N/A	N/A	Bridges and Solomon 2016	BRIDG16A and BRIDG16B (supplemental information, SI)

Method	Response	Results[1]	Remarks	Evaluation (score based on review)[2]	Klimisch score (from CSR Report)[3]	Reference	Reference ID
Review - Review of aquatic toxicity studies with D4 and approaches for risk assessment	N/A	Artificially closed systems are not appropriate testing methods due to increased sensitivity. Narcosis MoA and chemical activity (fugacity) explain the lack of toxicity caused by D4 to aquatic organisms when exposure occurs in environmentally realistic conditions.	No new data presented; analysis of existing aquatic toxicity data.	N/A	N/A	Fairbrother and Woodburn 2016	FAIRB16A
Review - Review and summary of the UK EA 2009 risk assessment to find suitable approach for REACH assessment.	N/A	N/A	This report is recaptures information presented in the UK EA report (Brooke et al. 2009; EA09A). The only notable comment states that the study with *Lumbriculus variegatus* with artificial sediment (WILDL09A) is considered less reliable than the study with natural sediment (SPRIN09A).	N/A	N/A	Peter Fisk Associates 2010	FISK10A
Review - Evaluation of usage data and patterns, physical chemical properties, toxicology, partitioning and degradation, methods of detection, and concentrations	N/A	Reviewed D4, D5, and D6. Review suggests no evidence of D4 and D5 trophic magnification in aquatic food webs, though some findings of bioconcentration and bioaccumulation. High concentrations in indoor air and biosolids near sources. Concentrations in water, sediment, and soil were below NOECs.	Review article by authors from Environment Canada discussing eco/toxicity, detection, occurrence, and fate of cVMSs. No new data presented. BUSER15A is a corrigendum (on the atmospheric half-life of D5) to WANG12A.	N/A	N/A	Wang et al. 2013a; Buser 2015	WANG13A; BUSER15A

Method	Response	Results[1]	Remarks	Evaluation (score based on review)[2]	Klimisch score (from CSR Report)[3]	Reference	Reference ID
Ecological risk assessment - Effects assessment was based on toxicity data, exposure assessment based on chemical properties and fate, modeling, and monitoring data	N/A	Comparison of predicted concentrations in the environment with NOEC values indicated large safety margins for water column and benthic organisms. Toxicity from aqueous exposure was characterized as requiring extended, continuous exposure and being limited to narcosis-like effects on behavior and survival. The authors concluded that the concentrations of D4 in aquatic ecosystems are expected to be low and transient in water and sediments. Comparison of predicted surface water concentrations with the lowest NOEC from toxicity studies indicated conservative 64-to 444-fold MOS for organisms exposed to the water column and 157- to 1,080-fold MOS for benthic organisms.	No new data. Monitoring data used were limited to 4 sewage treatment plants.	Reviewed by EA09A	N/A	Hobson and Silberhorn 1995	HOBSO95A
Ecological risk assessment - Acute and chronic toxicity data compared to critical target lipid body burdens (CLTBBs) as estimated by the target lipid model.	N/A	Validation of target lipid model. Findings suggest little evidence for risk of adverse effects of cVMS under present-day emission levels	This model, which resulted in an HC_5 CTLBB of 2.6 µg/mol lipid, was used in the ecological risk evaluation of Nusz et al. 2018 (NUSZ18A), which in turn forms the basis of the ecological risk assessment for D4. The analysis included the contribution from metabolites to the overall tissue residues using a food chain model calibrated to laboratory and field data.	N/A	N/A	Redman et al. 2012	REDMA12A

Method	Response	Results[1]	Remarks	Evaluation (score based on review)[2]	Klimisch score (from CSR Report)[3]	Reference	Reference ID
Ecological risk assessment - Probabilistic risk assessment (PRA) as well as deterministic approach to compare laboratory benthic chronic toxicity values to field sediment concentrations for D4, D5, and D6	N/A	Sediment concentration data (from field locations worldwide) were expressed as 95% cumulative distribution function (CDF) and compared to the invertebrate NOECs using either the hazard quotient (HQ) or 5% PRA approach. Neither approach resulted in overlap of exposure and effects for D4; thus, there is no risk.	No new data presented in this article. Used 5 benthic NOEC values (excluded WILDL09A).	N/A	N/A	Woodburn et al. 2018	WOODB18A

[1] Abbreviations used in the Endpoint column are defined as: LC50 – lethal concentration at which 50% mortality is observed; NOEC – no observed effect concentration; LOEC – lowest observed effect concentration; EC50 – effect concentration at which a response is induced in 50% of test organisms

[2] Ecotoxicological studies include a range of possible scores between 26 and 104. A higher score indicates lower reliability. Blue indicates high reliability, yellow indicates medium reliability, pink indicates low reliability, and no color indicates scoring not applicable.

[3] CSR 2018 (CSR18A)

[4] Functional solubility is defined as the maximal achievable solubility of D4 under the specific conditions and dilution water quality for a particular study.

Studies summarized directly from Bridges and Solomon (BRIDG16A) or CSR (CSR18A) when applicable; these studies are not found in the appendix.

6.2.4 Summary of Ecological Hazard

As described above, a number of aquatic toxicity studies have been conducted on D4. These include industry-sponsored studies as well as those described in the peer-reviewed literature; however, most of those publications are based on sponsored studies. These studies were mostly conducted in the 1980s to 2000s; no new toxicity data in the open literature were found in the post-2008 literature searches. The available studies report toxicity data for fish, aquatic invertebrates, algae, and benthic organisms.

D4 presents challenges for testing toxicity in aqueous test systems. D4 is very hydrophobic (log K_{OW} = 6.98) and with its low water solubility (0.074 mg/L), dissolving sufficient amounts of the compound in solution for toxicity testing is problematic. D4 is also highly volatile (vapor pressure 0.132 kPa); thus, D4 is likely to escape during conventionally run aqueous toxicity tests. To overcome these issues of testing D4 in water, Springborn conducted a series of toxicity tests in the 1990s that forced D4 into solution and prevented volatilization by maintaining the test system with no exposure to air. The concentrations of D4 measured in those tests approximated the limits of "functional" water solubility. While conducting toxicity tests in this manner may not be environmentally relevant, these data can be used to develop toxicity thresholds for water. However, the functional solubility of D4 in each test must be considered when determining the concentration at which adverse effects occurred.

Based on the laboratory toxicity tests described above, Nusz et al. (2018) developed toxicity thresholds for surface water, sediment and aquatic organism tissues. Nusz et al. (2018) evaluated the reliability and relevance of the available studies according to general guidance provided in EPA's Evaluation Guidelines for Ecological Toxicity Data in the Open Literature (U.S. EPA 2011b), and with considerations specific to the aims of this risk evaluation. Therefore, toxicological data for saltwater species were considered for context, but not used to derive toxicity thresholds, since the current risk evaluation is for freshwater systems. Because assessing D4 toxicity to aquatic receptors is complicated by its high volatility and low water solubility, studies which used closed systems were preferred to studies that used open systems. Nusz et al. (2018) selected the LC50 from prolonged acute tests to represent the acute toxicity threshold for surface water. These authors also derived the chronic endpoint as the geometric mean of the

NOEC and the LOEC, or the NOEC where the chronic LOEC value could not be calculated. Aqueous (surface water) thresholds were developed separately for fish and invertebrates, whereas sediment thresholds were developed for benthic invertebrates only. The most sensitive freshwater species were selected for the prolonged acute and chronic values (Springborn 1990c,d, 1991c; Table 6-9). Far fewer studies were available that exposed benthic invertebrates to D4 in sediments. The lowest bounded LC50 from a 14-day sediment test was used for the acute benthic invertebrate value (Springborn 1991a). Of the three chronic sediment toxicity tests, the chronic value from the study that used natural sediment (Springborn 2009) was selected over two studies that used artificial sediment (Wildlife International, Ltd. 2008b, 2009). Since organic carbon content affects the bioavailability and hence toxicity of organic compounds like D4, the sediment thresholds for benthic organisms are presented on a total organic carbon basis (i.e., mg D4/kg dry weight total organic carbon). The toxicity thresholds presented in Nusz et al. (2018) (Table 6-9) are used in the ecological risk characterization for D4.

Table 6-9. Aquatic and sediment toxicity thresholds derived by Nusz et al. (2018)

Exposure Duration	Receptor	Basis	Aquatic Threshold (µg/L)[a]	Sediment Threshold (mg/kg, dry weight)[a]	Sediment Threshold (mg/kg dry weight TOC)[b]	Aquatic / Sediment Activity Threshold (unitless)[c]
Prolonged Acute	Fish	14-day LC50	10 (SPRIN90D)	NA	NA	0.15[d]
	Benthic Invertebrate	14-day LC50	NA	170 (SPRIN91A)	7,400	6.6[e]
Chronic	Fish	93-day NOEC	4.4 (SPRIN91C)	NA	NA	0.068[d]
	Aquatic Invertebrate	21-day MATC/ChV	11 (SPRIN90C)[f]	NA	NA	0.19[d]
	Benthic Invertebrate	28-day ChV	NA	15.7 (SPRIN09A)	710	0.63[e]

[a] from selected toxicity test; reference is provided in parentheses.
[b] The sediment thresholds on a dry weight basis were converted to TOC basis using the reported TOC values from the studies (2.3% for the prolonged acute and 2.2% for the chronic value). Resulting values were rounded to two significant figures.
[c] Activity thresholds were calculated with an Activity Calculator created by F. Gobas and colleagues at Simon Fraser University (Gobas et al. 2015b). The calculator is used to express concentrations of chemicals in various media on a common basis in terms of their thermodynamic activity so that concentrations in various media can be compared.
[d] To be used for comparison to activities of D4 in field-collected water samples.
[e] To be used for comparison to activities of D4 in field-collected sediment samples.
ChV = chronic values; these values were calculated by Nusz et al (2018) as the geometric mean of the study NOEC and LOEC. MATC = maximum acceptable toxicant concentration.
[f] Value is conservative relative to study re-evaluation which resulted in NOEC ≥ 15 µg/L

In addition to these water and sediment thresholds which are based on the systematic review of laboratory toxicity tests, two other metrics of toxicity are used to evaluate risk to ecological receptors from D4 (Nusz et al. 2018). One of these metrics is the CTLBB of 2.6 µmol/g lipid, which is the value developed for cVMSs by Redman et al. (2012) (see above for description of

Redman et al. 2012). D4 concentrations measured in field aquatic organisms can be compared to this CTLBB value; if they are above this level, toxicity could result. The other metric that was used in the D4 ecological risk assessment is the chemical “activity”, which allows for a direct comparison of exposure and toxicity data (Gobas et al. 2015b). The chemical activities were calculated by Nusz et al. (2018) for each threshold derived from the laboratory toxicity tests (Table 6-9) using an Activity Calculator created by Gobas et al. (2015b). Chemical activities in water or sediment are the ratio of a concentration and the chemical's solubility, adjusted for salinity, amount of particulate matter, and carbon content. Activity in sediment also accounts for partitioning between the water compartment and organic carbon. Activities in biota are the ratio of the lipid-based concentration and the apparent solubility of the chemical in lipid, which is based on the compound's K_{OW} and its aqueous solubility value.

7 Risk Characterization

7.1 Human Health Risk Characterization

7.1.1 Overview

The human health risk characterization for D4 integrates the human health hazard and exposure assessments into quantitative assessments of risk for worker, consumer, and general population exposures including potentially exposed or susceptible subpopulations identified as pregnant or lactating women, infants and children, and subsistence fisherman.

This risk characterization is based on the results of a global human health risk assessment published by Gentry et. al. (2017) and incorporates global exposure information combined with a Monte Carlo analysis to determine the MOEs for significant routes of exposure. The exposure data used by Gentry et al. (2017) is substantially similar to the exposure assessment conducted by SEHSC for Health Canada (SEHSC 2008b; the Canadian Assessment; and as updated in the Updated Assessment) as summarized in the Exposure Assessment, Section 5 of this document. BMD modeling was used to determine a POD for risk characterization, utilization of a PBPK model was included to estimate internal dose metrics based on worker, consumer, and general population exposures, and an MOE evaluation was used to compare the estimates of exposure with the benchmark POD (level of total uncertainty). Due to the specific pharmacokinetic behaviors of D4 (high lipophilicity, high volatility, low blood-to-air partition coefficients, extensive metabolic clearance), the use of a published multi-route PBPK model (McMullin et al. 2016) was essential in providing a dose metric that reflects these processes.

Both sentinel and aggregate exposures are also considered in this risk characterization. Sentinel exposure is defined as the exposure to a single chemical substance that represents the upper plausible bound of exposure relative to all other exposures within the broad category of similar or related exposure. Aggregate exposure means the combined exposures to an individual from single chemical substance across multiple routes and across multiple pathways.

This risk characterization is conservative because exposures to non-TSCA regulated products, namely personal care products as formulated by workers, personal care products, cosmetics, and over-the-counter (OTC) medication (vapor rub) for consumers, and food contact materials (anti-foam agents, baby bottle nipples), cosmetics (lipstick), and OTC medications (anti-gas) for the general population, are included in the assessments by Gentry et al. (2017). Exposures to personal care products as evaluated by Gentry et al. (2017) are used herein as surrogates for TSCA-relevant exposures (e.g., household care products) and are considered conservative because the use as household care products would result in lower exposures (e.g., they are not used daily nor applied directly to the body).

The results of this risk assessment determined that MOEs were greater than the benchmark MOE of 100 for workers, consumers, and the general population who may be exposed to D4 either in the workplace, through the use of consumer products containing D4, or to D4 released in the environment. The lowest MOE (15,000; 150-fold higher than the benchmark MOE) was estimated for workers engaged in skin care product formulation. The aggregate MOEs (MOE of 12,000 for men, 26,000 for women) were similar to that of workers, and likewise well above the benchmark MOE. Therefore, a determination of no unreasonable risk of injury to human health can be made for the uses of D4 covered in this risk evaluation (discussed in Section 8).

7.1.2 Point of Departure

The approach of Gentry et al. (2017) to hazard identification and estimation of a POD is outlined in Section 6.1 Human Health Hazards. As described, the POD is based on the results of the two-generation inhalation reproduction study in rats. In short, benchmark dose modeling was used to determine a POD from this toxicology study and PBPK modeling was executed with human parameter values for both physiological parameters (such as ventilation rate or cardiac output) and for D4-specific parameters to develop estimated internal dose-metrics that were unique to the receptor, route of exposure, and exposure pattern. The NOAEC for the POD was 300 ppm, however the more conservative BMDL endpoint of 125 ppm based on benchmark dose modeling (BMD) was the basis for the POD. PBPK modeling was then conducted to determine the internal dose level, which was used in this risk characterization. As indicated by Gentry et al. (2017), no

correction for absorption or bioavailability was necessary since the PBPK model already includes data related to these parameters.

The POD for all populations (including children), durations, and routes of exposure was expressed in terms of the human equivalent dose [HED] (internal dose) and is 30 mg-hr/L blood/day, based on the AUC of free D4 in the blood and on the worst-case assumption of continuous exposure. As explained further below, an additional 10X uncertainty factor is added to the Benchmark MOE to account for the current PBPK model (McMullin et. al. 2016), which is not designed to estimate internal dose metrics for children or pregnant/lactating women.

7.1.3 MOE Approach

The MOE is the ratio of the POD dose divided by the human exposure dose. The MOE is then compared to the benchmark MOE to characterize potential risk. If the MOE exceeds the benchmark MOE, this indicates that risks to human health are not expected. The following equation was used to calculate the MOE:

$$MOE = POD/Exposure$$

7.1.4 Benchmark MOE

Conservatively, Gentry et al. (2017) used a benchmark MOE of 1000. This value includes an uncertainty factor of 10X for intra-human variability, 1X uncertainty factor for extrapolation from animal-to-human allowing for uncertainties in pharmacodynamics across species (it is expected that women would be less sensitive than the rodent to modifications in hormone balance), 10X uncertainty factor for the use of tumor rather than precursor data, and 3X uncertainty factor or remaining sources of uncertainty related to the database. This last uncertainty factor was applied due to lack of a chronic inhalation toxicity/carcinogenicity study in multiple species. Therefore, Gentry et al. (2017) anticipated that any MOE greater than 1000 should indicate negligible risk of adverse effects due to the exposure scenarios being considered.

In contrast to the benchmark MOE employed by Gentry et al. (2017) and as summarized in Section 6, a benchmark MOE of 100 was considered the best available science based on a 10X

uncertainty factor for intra-human variability, 1X uncertainty factor for extrapolation from animal-to-human (based on the use of PBPK data), and 10X uncertainty factor for remaining sources of uncertainty related to the database. This latter 10X uncertainty factor accounts for the current PBPK model (McMullin et al. 2016) which is not designed to estimate internal dose metrics for children or pregnant/lactating women. Thus, for this risk characterization, an MOE greater than 100 would indicate no significant risk of adverse effects for the exposure scenarios being considered.

7.1.5 Exposures Evaluated in the Risk Characterization

Exposures and thus MOEs (risks) are evaluated for workers (the sentinel population), consumers, and the general population. As detailed in Section 5.1, MOEs are determined for the following worker exposures:

- Inhalation by silicone workers
- Inhalation by formulators of personal care products (not TSCA relevant); as conservative surrogate for all TSCA-relevant exposures (manufacturing, processing, and formulation of industrial use products)
- Inhalation by barbers and beauticians, and by office workers; not TSCA relevant
- Dermal contact by barbers and beauticians; not TSCA relevant.

For consumers, MOEs are calculated for inhalation and dermal contact during use of personal care products (not TSCA relevant), with these products serving as a surrogate for TSCA relevant housecare products. For the general population, the Risk Characterization evaluates the inhalation of indoor and outdoor air. The rationales for exposure pathways included in the Risk Characterization are presented in Section 5.1. In summary, the decision of which pathways to carry forward is based on the prioritization work by Gentry et al. 2017.

As indicated in Section 5, the AUC exposure estimates as estimated by Gentry et al. 2017 and presented in Table 5-3 (worker), Table 5-8 (consumer), and Table 5-12 (general population) are the exposure values used in this Risk Characterization. These exposures are expressed in terms of internal dose levels (in mg-hr/L blood/day) based on PBPK modeling.

As discussed, in Section 6.1.9, further update and refinement of this multi-route pharmacokinetic model is underway and expected to be submitted for publication by early 2020. This model update will include a conversion of the model from asclX to the R software platform and has incorporated additional mechanistic pharmacokinetic data on both Fischer 344 and Sprague Dawley rats that uncovered pharmacokinetic differences in the two strain of rats as well as the need for a more refined model description of the MLP handling into the hepato-lipid recirculation. To evaluate the potential impact of any model update on the AUC exposure estimates as estimated by Gentry et al. 2017 and presented in Table 5-3 (worker), Table 5-8 (consumer), and Table 5-12 (general population). Gentry et al. 2019 identified the scenario that provided the lowest MOE in Gentry et al. 2017 (male skin care workers – MOE 1500; 10-fold less than in this Risk Evaluation due to the higher benchmark MOE used by Gentry et al. 2017), assuming that all other MOE would scale linearly. They also compared the simulations from the current version of the multicompartment PBPK model (Campbell et al. 2017) to the dose metrics for the male skin care worker reported in Gentry et al. (2017).

The dose metric for male skin care workers (average free D4 of workers exposed 50 weeks/year, 5 days/week, 8 hrs/day to 2.44 ppm D4) was reported in Gentry et al. (2017) to be 0.144 mg*h/L/day. The current version of the multicompartment PBPK model (Campbell et al., 2017) yields a dose metric of 0.186 mg*hr/L/day for the worker scenario prior to incorporating the MLP revisions. The exact reason for this increase is not known; however, changes were made to model since the simulations in Gentry et al. 2017 were conducted that involve the distribution of D4 in the liver to accommodate the liquid diet study and may have impacted the free concentration in human blood. The result of this increase in the human dose metric would be to lower the MOE for male skin care workers from 1500 to 1159 (would be 15000 and 11590 in this Risk Evaluation).

After including the MLP revision for rat and human, the dose-metric for the rat was lowered approximately 3% while the male skin care worker was essentially unchanged (0.186 mg*hr/L/day). This results in a slightly lower (by 3%) MOE of 1125 for male skin care workers (would be 11250 in this Risk Evaluation).

While the changes in these dose metrics with the application of the MLP results in a 30% reduction in the MOS, it does not change the conclusions in Gentry et al. (2017) that all MOE are greater than the benchmark MOE of 1000 (100 in this Risk Evaluation).

7.1.6 Risk Characterization

The risk characterization calculates the MOE by comparing the POD to the calculated exposure. This comparison is presented here for the same exposure categories defined in Gentry et al. (2017), using the same POD. The difference is that the benchmark MOE in this risk evaluation is 100 versus the 1000 used by Gentry et al. (2017).

7.1.6.1 Worker Risk Characterization

The MOE estimates for workers potentially exposed to D4 are presented in Table 7-1.

As shown, the estimated inhalation AUCs are highest (and the MOEs lowest) for the workers involved in the formulation of skin care products, particularly in men. Comparison of the exposure AUC for this worker category to the POD resulted in an MOE of 15,000. The MOE values for inhalation exposure for skin care formulators are 7 to 28 times higher (risks less) than for silicone workers and formulators of other products. Therefore, the lowest MOE of 15,000 is conservative for all manufacturers, processors and formulators of D4 (Table 7-1).

The MOEs for non-TSCA relevant inhalation exposures for barbers/beauticians and office workers are 40 to 500 times higher (risks less) than those for skin care formulators.

In summary, the lowest occupational MOE (highest risk) is for the inhalation exposure of workers engaged in the formulation of skin care products.

Table 7-1. Margins of Exposure (MOEs): Occupational dermal and inhalation exposure

Worker	MOEs	
	Men	**Women**
Dermal		
Barbers and Beauticians		
5-days	2,450,000	1,730,000
4-days	1,930,000	1,370,000
Inhalation		
Antiperspirant (formulation)	110,000	350,000
Skin Care (formulation)	**15,000**	**47,000**
Hair Care (formulation)	3,110,000	9,670,000
Silicone workers	170,000	550,000
Barbers and Beauticians		
5 days	600,000	1840,000
4 days	610,000	1860,000
Office Worker		
5 $\mu g/m^3$ (0.000383 ppm)	13,000,000	24,000,000
10.2 $\mu g/m^3$ (0.000781 ppm)	650,000	12,000,000

Lowest MOE's are in bold.

7.1.6.2 Consumer Risk Characterization

All consumer MOEs were larger than those of workers, indicating even lower risk to consumers. As presented in Table 7-2, the smallest MOE from inhalation exposure for consumers was 130,000 (use of roll-on deodorant in women) and the smallest MOE based on dermal exposure was 95,000 (use of hand lotion by women), noting again that personal care products were used as worst-case surrogates for household care products in this Risk Evaluation. Even higher MOEs would be expected for household care products, since they are used less frequently and not intentionally applied to the body. In addition, the Benchmark MOE includes a 10X uncertainty factor to account for the current PBPK model (McMullin et al. 2016), which is not designed to estimate internal dose metrics for children or pregnant/lactating females.

For child consumers, a qualitative comparison of exposures to those for adults, based on Table 5-9 from Gentry et al. 2017, was undertaken. Based on this comparison, most child exposures are comparable to those for adults, or are within one order of magnitude. The one exception is the use of shampoo for which child exposures are up to 10,000 times greater than for adults. Since

the adult MOEs for shampoo are 10^{10}, the exclusion of child consumers from the MOE analysis does not affect the conclusion that D4 does not pose a health risk to this population.

Overall, the consumer analysis indicates that typical consumer usage of D4-containing products would pose no unreasonable risk.

Table 7-2. Margins of Exposure (MOEs): Exposure from selected consumer products

Product[a]	**MOEs**	
	Men	**Women**
Dermal Exposures		
Solid Deodorant	2.4×10^7	1.8×10^6
Roll-on Deodorant	1.8×10^7	1.2×10^7
Aerosol Deodorant	2.1×10^7	2×10^6
Shampoo	4×10^{10}	1×10^{10}
Conditioner (Rinse-out)	4.1×10^7	1.4×10^6
Conditioner (Leave-in)	8.3×10^6	3.4×10^6
Hair spray (aerosol)	3×10^{10}	1.3×10^{10}
Hair spray (pump)	2×10^{10}	9×10^9
Moisturizer	3.1×10^6	1.2×10^6
Foundation	N/A	550,000
Night cream/Under eye cream	N/A	4.8×10^6
Lipstick (6 days)	N/A	3.9×10^6
Lipstick (5 days)	N/A	9.6×10^6
Mascara	N/A	2×10^6
Hand/body lotion	**120,000**	**95,000**
Sunscreen	2.2×10^9	9.5×10^8
Nail care	N/A	3.3×10^7
After-shave gel	740,000	N/A
Soothing vapor	3.9×10^{10}	1.6×10^{10}
Inhalation Exposures		
Solid Deodorant	1.1×10^7	9.8×10^6
Roll-on Deodorant	**140,000**	**130,000**
Aerosol Deodorant	280,000	250,000
Hair spray (aerosol)	720,000	630,000
Hair spray (pump)	720,000	630,000
Moisturizer	720,000	630,000
Foundation	N/A	630,000
Hand/body lotion	720,000	630,000
Sunscreen	720,000	630,000
Nail care	N/A	630,000
After-shave gel	720,000	N/A
Soothing vapor	1×10^8	1.9×10^8

[a] Personal care products are not relevant under TSCA, but are used here as worse case surrogates for TSCA relevant household care products; Lowest MOE's are in bold.

7.1.6.3 General Population Risk Characterization

All MOEs for the general population were larger than those of consumers and the sentinel population (workers), indicating less risk for the general population (Table 7-3). The smallest MOEs were for inhalation by men: 1,500,000 for indoor air and 7,800,000 for outdoor air. In addition, the Benchmark MOE includes a 10X uncertainty factor to account for the current PBPK model (McMullin et al. 2016), which is not designed to estimate internal dose metrics for children or pregnant females.

For children in the general population, a qualitative comparison of exposures to those for adults, based on Table 5-9 from Gentry et al. 2017, was undertaken. Based on this comparison, the inhalation child exposures are comparable to those for adults, or are within one order of magnitude. Since the adult MOEs for inhalation are 10^6-10^7, the exclusion of children in the general population from the MOE analysis does not affect the conclusion that D4 poses no unreasonable risk to this population. The estimation of MOE values for the general population from environmental media (soil, drinking water, fish, other food [plant-based crops, meat, milk]), for infants drinking breastmilk or for subsistence fisherman was not carried out since the associated exposure potentials were two orders of magnitude less than the exposure representing the greatest exposure to D4 through consumer use (e.g. body lotion for adults), and therefore would not impact the overall risk characterization.

Table 7-3. Margins of Exposure (MOEs): Inhalation exposure for general population

Residential 20–59 yr olds

Location	MOEs	
	Men	Women
Indoor (10 µg/m^3)	1,500,000	2,780,000
Outdoor (0.2 µg/m3)	7,800,000	13,000,000

7.1.7 Sentinel and Aggregate Risks

Sentinel exposure is defined as the exposure to a single chemical substance that represents the upper plausible bound of exposure relative to all other exposures within the broad category of similar or related exposure. Workers represent this upper plausible bound of exposure, and the MOEs for workers are the lowest; therefore, this group serves as a sentinel population.

Aggregate exposure means the combined exposures to an individual from single chemical substance across multiple routes and across multiple pathways. The results from the aggregate risk characterization are included in Table 7-4. The aggregate assessment uses all conservative exposures (occupational-inhalation, consumer-dermal, consumer-inhalation, and general population – inhalation). The results of the aggregate MOEs are greater than the benchmark MOE of 100. The aggregate MOE assessment resulted in MOE values of 12,000 for men and 26,000 for women (Table 7-4.).

Table 7-4. Estimates of worst-case aggregate margins of exposure (MOEs)

Exposure Scenario	**MOEs**		**Exposure = POD*/ MOE** **mg-hr/L blood/day**		**Aggregate MOE = POD*/Aggregate exposure** **mg-hr/L blood/day**	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
Occupational – inhalation[1]	15,000	47,000	0.002	0.0006	-	-
Consumer dermal	120,000	95,000	0.00025	0.0003	-	-
Consumer inhalation	140,000	130,000	0.0002143	0.0002308	-	-
General Population - inhalation	1,500,000	2,780,000	0.00002	0.0000108	-	-
Aggregate	-	-	0.0024843	0.0011416	12,000	26,000

*POD = 30 mg-hr/L blood/day

[1] Occupational inhalation exposure D4 manufacturing/processing/formulation is included in this assessment because it is greater than occupational dermal exposure from barber/beauticians and a worker is not going to be both a barber/beautician and work in D4 manufacturing/processing/formulation

7.1.8 Uncertainty

Uncertainties related to the POD and the exposure estimates are discussed in the Section 5.1 and Section 6.1, respectively. For the risk characterization, there is little to no uncertainty in the conclusion of no unreasonable risk of adverse effects based on the use of conservative exposure pathways as surrogates for TSCA-relevant exposures and a conservative POD. Specifically, for exposure, the sentinel population of workers was based on the highest potential exposure (formulation of skin care products) to represent TSCA-relevant exposures (manufacturing,

processing and formulation of industrial use products). Additionally, consumer exposures were also based on the use of personal care products as the highest potential surrogate for exposure to household products. Lastly, exposure to the general population included both conservative assumptions and surrogate uses. Even when aggregated, there is no unreasonable risk.

7.1.9 Summary of Human Health Risk Characterization

Risks to human health are not unreasonable based on estimating the conservative sentinel exposure, which results in MOEs at least 150-fold more than the benchmark MOE of 100. MOEs for consumers and the general public who may be exposed to D4 were even higher, similarly indicating no unreasonable risk of adverse effects. Aggregate risk assessments also indicate no unreasonable risk, with aggregate MOEs at least 120-fold more than the benchmark dose.

7.2 Ecological Risk Characterization

7.2.1 Overview

The information available for use in the risk characterization includes multiple lines of evidence (LoEs) (Suter et al. 2017). The LoEs include 1) comparing D4 concentrations measured in environmental media to toxicity thresholds derived from laboratory bioassays with sensitive aquatic receptors (fish, invertebrates and plants); 2) comparing D4 concentrations measured in biota tissue to the CTLBB derived from the target lipid model (TLM); 3) fugacity-based chemical activity assessment; and 4) assessing benthic community metrics. A fifth LoE used in this assessment is the consideration of bioaccumulation potential.

Of the five LoEs, the first three LoEs use metrics of toxicity thresholds to evaluate the ecological hazards of D4 to aquatic receptors. The data and approaches used to derive these thresholds were discussed in Section 6.2. Thresholds of toxicity to water column and sediment organisms were developed by a systematic review of laboratory toxicity tests conducted with representative species, a metric of critical body residues of D4 was established using a TLM assessment previously developed for D4, and chemical activity was calculated at toxicity threshold concentrations.

To assess potential exposures of D4 to aquatic receptors, cumulative distributions of concentrations of D4 measured in water, sediment, and tissues (fish and benthic invertebrate) samples were created. These distributions of exposure values quantified the expected range and variability of real-world exposures. Only data from the ECA monitoring investigation was used due to its systematic and designed sampling program, which was designed by stakeholders and approved by the EPA. The distributions were then compared to the appropriate toxicity threshold values (e.g., derived from toxicity tests with ecological receptors) to evaluate the probability of exposures exceeding levels expected to cause toxicity.

Concentrations below the LOQ, i.e., "non-detects" or censored observations, are important to include in risk calculations because they represent a valid component of the expected exposure concentration distribution in the field, which is unrelated to the analytical method reporting limit. As these concentrations cannot be calculated directly given analytical method limitations, they were estimated using the regression on order statistics method (Singh and Singh 2013). This method involves fitting a regression line to a normal probability plot of uncensored observations and then imputing values for observations below the LOQ in the tail of the assumed normal distribution.

The cumulative distributions for each media were compared to relevant toxicity thresholds or integrated with effects distributions to evaluate risk for ecological receptors from the various exposure pathways.

For LoE 1 (comparison to toxicity thresholds from laboratory toxicity tests), the toxicity threshold values for benthic invertebrates were converted from units of mg/kg sediment to units of ng/g sediment for direct comparison with the measured concentrations in sediment. Furthermore, the toxicity thresholds selected for the sediment compartment were divided by the proportion of TOC content of the sediments used in the toxicity tests to derive TOC normalized thresholds (ng/g TOC) for comparison to the TOC normalized concentrations measured in field sediment.

For LoE 2, the HC5 CTLBB (the level at which no narcosis effects would be expected for 95% of aquatic organisms; 2.6 μmol/g lipid) derived by Redman et al. (2012) was compared to

cumulative distributions of tissue concentrations of D4 in fish and benthic invertebrates measured in field collected organisms to determine the probability of tissue concentrations reaching the level required to cause toxicity. Lipid-normalized concentrations of D4 in tissue were converted to units of μmol/g lipid, using the molecular weight of D4 (297 g/mol), before comparison with the HC5 CTLBB.

For LoE 3, the online Activity Calculator version 1.2 (Gobas et al. 2015b) was used to calculate activities for the ECA field samples using measured concentrations of D4 in water, sediment, benthic invertebrates, and fish. The activities of the ECA field samples were then compared to the activities calculated for D4 at toxicity threshold concentrations as an additional approach to determining whether environmental exposures were at levels high enough to cause toxicity. For both the ECA field data and thresholds, the water solubility (56.2 μg/L) used for calculating activities was derived from a standard water solubility test (Varaprath et al. 1996). This solubility is much higher than would be expected to occur in toxicity tests (approximately 6 to 30 μg/L; see ecological hazard assessment section) and even higher than what would be expected under environmentally relevant conditions, where volatilization of D4 would be greater. Thus, the calculated activities for the ECA field data and the toxicity thresholds are lower (i.e., signifying less saturation) than would result from calculation with functional solubilities. The approach used is considered conservative, as under this approach, calculated activities for toxicity thresholds would be closer to calculated activities for field samples than one could expect if using the functional solubilities available from the toxicity tests.

For LoE 4, the benthic community and habitat was evaluated. Assessments of aquatic communities have been used for several decades to determine if the integrity of receiving water ecosystems is degraded (Barbour et al. 1999; Wetzel 2001). Benthic community responses often are described in terms of changes to the community structure (e.g., species abundance and diversity), ecological functions, or species' tolerance to pollutants. Descriptive metrics were calculated for each site and event (when $n \geq 100$ organisms) to provide information on the taxonomic composition, stressor tolerance, and organism condition (Flotemersch et al. 2006) of the benthic community. The sampling station and the method of benthos collection were dictated by site characteristics. For example, if there was no substrate amenable to benthos habitation

(e.g., bedrock, consolidated clay), then it was not sampled. Any habitat capable of supporting benthic macroinvertebrates was sampled, including submerged vegetation, woody debris, and sediments. Sampling this range of habitat conditions dictated a range of sampling methods be utilized to optimize organism collection and site characterization. While this approach ensured a comprehensive evaluation of the benthic community at each discharge site, it precluded the ability to make statistical comparisons between sites. The tolerance measure, Modified Hilsenhoff Biotic Index (HBI; Plafkin et al. 1989; Bode et al. 1991), was calculated using tolerance values compiled from Mandaville (2002). Additional metrics presented include common richness (total number of taxa, Ephemeroptera Plecoptera Trichoptera [EPT] number) and composition measures (%EPT, %Order Diptera [true flies]), reflecting the diversity and condition of the assemblage (Barbour et al. 1999). Evaluations of the benthic macroinvertebrate communities are based on the assumption that nondegraded streams would be composed of many different taxa, including pollution intolerant taxa like the mayflies, stoneflies and caddisflies (i.e., the EPT). Polluted or stressed aquatic environments are often dominated by pollution tolerant species like chironomids (order Diptera) and aquatic worms. Additionally, in situ habitat conditions are extremely important in controlling population and community profiles and can be driven by both natural and anthropogenic factors (Barbour et al. 1999). This benthic qualitative assessment utilized the dominant habitat characteristics driving benthic macroinvertebrate population distributions, including sediment substrate type (and sediment particle size), stream cover, and stream morphology. These habitat traits were recorded during field sampling using site diagrams and photographs and notes and were used to develop a simple benthic quality index. Habitat and water flow are major drivers in determining the quality and community composition of fish and benthic invertebrate communities (Patrick 1988). As such, they can be major stressors, overestimating the effects of chemical exposures. In a multiple-LoEs approach, it is essential these physical factors and potential stressors be considered.

For LoE 5, a qualitative assessment of bioaccumulation potential is performed. This endpoint is also discussed in Section 3.3.5.

7.2.2 LoE 1: Comparison of D4 Water and Sediment Concentrations to Toxicity Thresholds

Table 7-5 summarizes the toxicity threshold values selected for water column (fish and aquatic invertebrates) and benthic organisms used in the risk characterization, with the aquatic thresholds (in µg/L) and the sediment threshold (in ng/g dry weight TOC) used in LoE 1, and the activity thresholds used in LoE 3. As part of LoE 1, the field surface water and sediment concentrations are compared to the thresholds for these respective media. A detailed summary of all aquatic toxicity tests with D4 is provided in Section 6.2.

Table 7-5. Summary of toxicity thresholds for ecological receptors (Nusz et al. 2018)

Exposure Duration	Receptor	Basis	Aquatic Threshold (µg/L)[a]	Sediment Threshold (mg/kg dry weight)[a]	Sediment Threshold (ng/g dry weight TOC)[b]	Aquatic/Sediment Activity Threshold (unitless)[c]
Prolonged Acute	Fish	14-day LC50	10	NA	NA	0.15[d]
	Benthic Invertebrates	14-day LC50	NA	170	7,400,000	6.6[e]
Chronic	Fish	93-day NOEC	4.4	NA	NA	0.068[d]
	Aquatic Invertebrate	21-day MATC/ChV	11[f]	NA	NA	0.19[d]
	Benthic Invertebrate	28-day ChV, *Lumbriculus variegatus* in natural sediment	NA	15.7	710,000	0.63[e]

Notes:
[a] Aquatic used in LoE 1; from selected toxicity test.
[b] Used in LoE 1; The sediment thresholds on a dry weight basis were converted to TOC basis using the reported TOC values from the studies (2.3% for the prolonged acute and 2.2% for the chronic value). Resulting values were rounded to two significant figures.
[c] Used in LoE 3; Activity thresholds were calculated with an Activity Calculator created by F. Gobas and colleagues at Simon Fraser University (Gobas et al. 2015b). The calculator is used to express concentrations of chemicals in various media on a common basis in terms of their thermodynamic activity so that concentrations in various media can be compared.
[d] Used for comparison to activities of D4 in field-collected water samples.
[e] Used for comparison to activities of D4 in field-collected sediment samples.
ChV = chronic values; these values were calculated by Nusz et al. 2018 as the geometric mean of the study NOEC (no-observed [f] effect concentration) and LOEC (lowest-observed effect concentration). MATC = maximum acceptable toxicant concentration
[f]Value is conservative relative to study re-evaluation which resulted in NOEC ≥ 15 µg/L.

Cumulative distributions of concentrations of D4 measured in water and sediment samples for each site type, as well as overall medians and 95th percentiles of the data for all three site types combined, compared to toxicity thresholds derived from toxicity tests with ecological receptors are shown in Figure 7-1 and Figure 7-2, respectively. These comparisons indicate no exceedances of toxicity thresholds by D4 concentrations measured in water and sediment samples collected in the mixing zones downstream of discharges from on-site treatment sites or

from municipal WWTPs receiving residential or industrial discharges. D4 concentrations measured in water were all at least an order of magnitude less than the lowest toxicity threshold for fish. Sediment concentrations from samples collected at residential and industrial municipal WWTP sites were more than two orders of magnitude below the lowest toxicity threshold for benthic invertebrates, and more than half of the sediment concentrations from samples collected downstream of discharges from on-site treatment sites were two orders of magnitude less than the lowest threshold. This LoE indicates that surface water and sediment concentrations from samples collected downstream from MPF facility discharges following on-site wastewater treatment and industrial or residential municipal WWTPs are all below applicable toxicity thresholds.

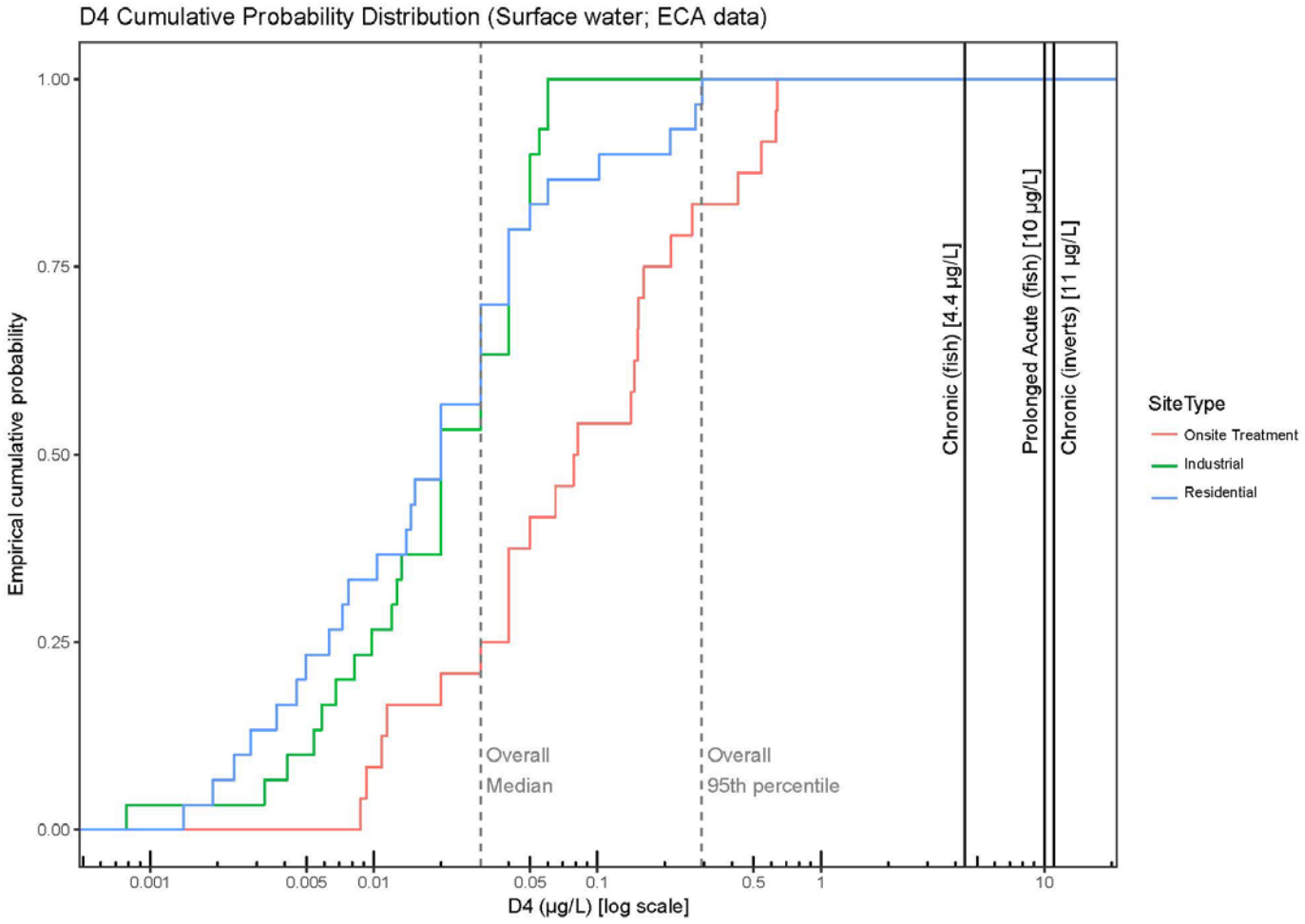


Figure 7-1. Comparison of D4 concentrations in water to toxicity thresholds for freshwater receptors in the water column.

Note: The overall median and 95th percentile presented are for all three site types combined.

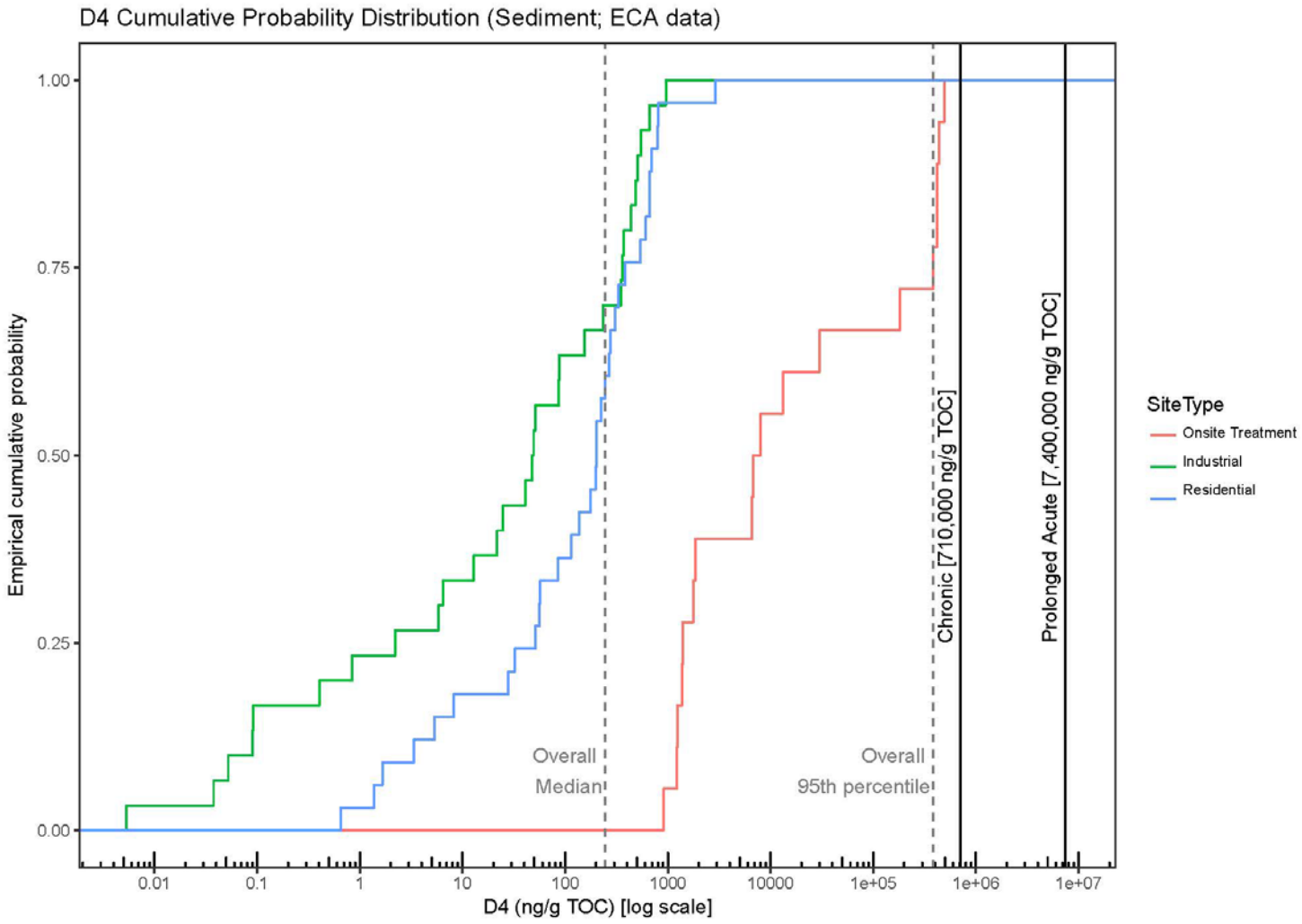


Figure 7-2. Comparison of carbon-normalized D4 concentrations in sediment to carbon-normalized toxicity thresholds for freshwater benthic invertebrates.

Note: The overall median and 95th percentile presented are for all three site types combined.

7.2.3 LoE 2: Comparison of D4 Tissue Concentrations to TLM CTLBB

The second LoE compares cumulative distributions of lipid normalized tissue concentrations of D4 measured in field-collected fish and benthic organisms to the tissue concentration below which no narcosis effects would be expected for 95% of aquatic organisms (HC5 CTLBB) (Figure 7-3 and Figure 7-4, respectively). No D4 concentrations in fish or benthic invertebrate tissue exceeded the HC5 CTLBB, signifying that the tissue concentrations in aquatic organisms collected downstream of municipal WWTP discharges and discharges of D4 from on-site treatment sites were too low to cause toxicity. This finding is consistent with results reported in

Redman et al. (2012), who also found no exceedances of the HC5 CTLBB by concentrations measured in biota collected from Lake Pepin, Minnesota; freshwater lakes in Sweden; and the inner and outer Oslo Fjord, Norway.

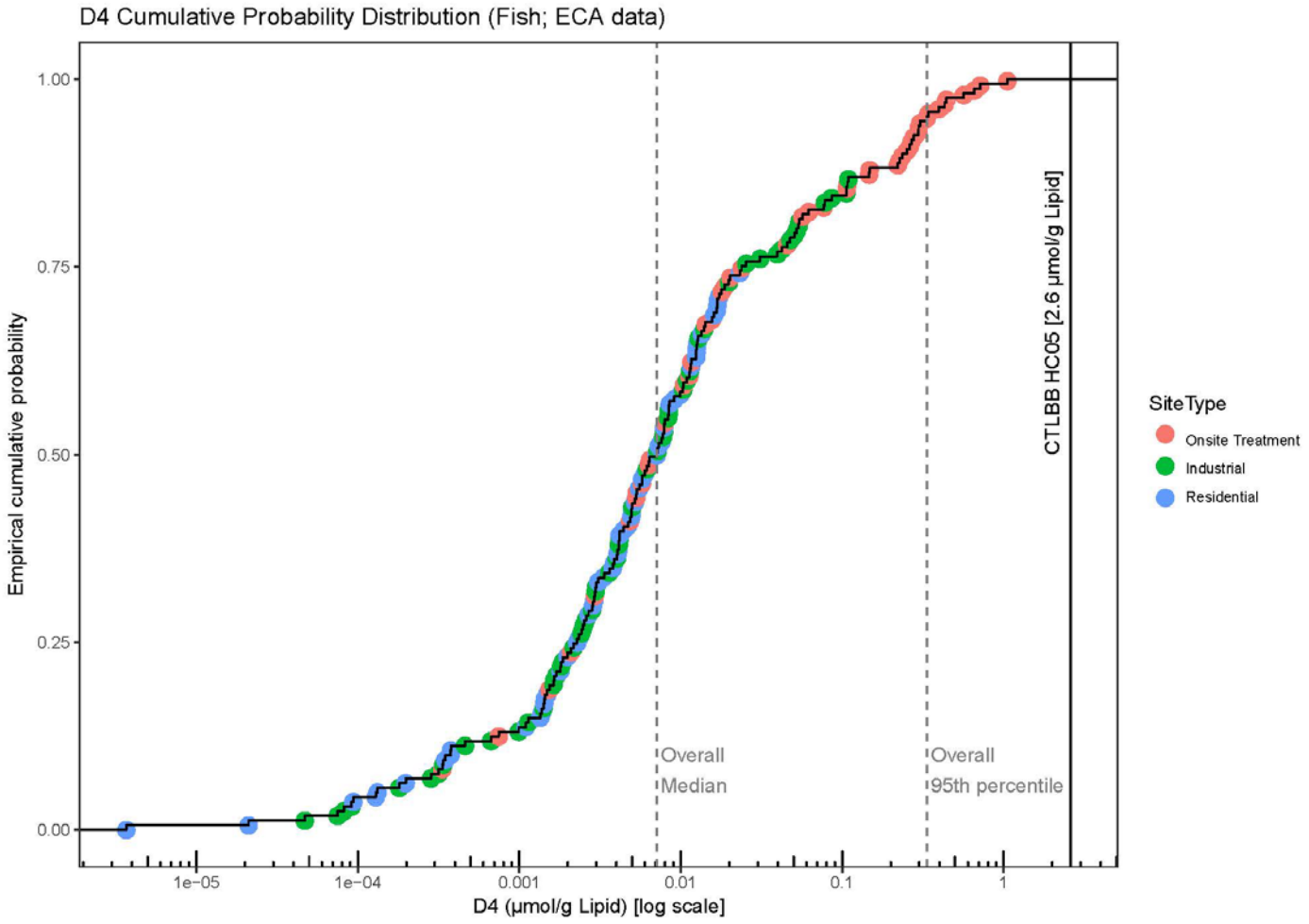


Figure 7-3. Comparison of lipid-normalized D4 concentrations in fish tissues to HC_5 critical tissue lipid body burden.

Note: The overall median and 95th percentile presented are for all three site types combined.

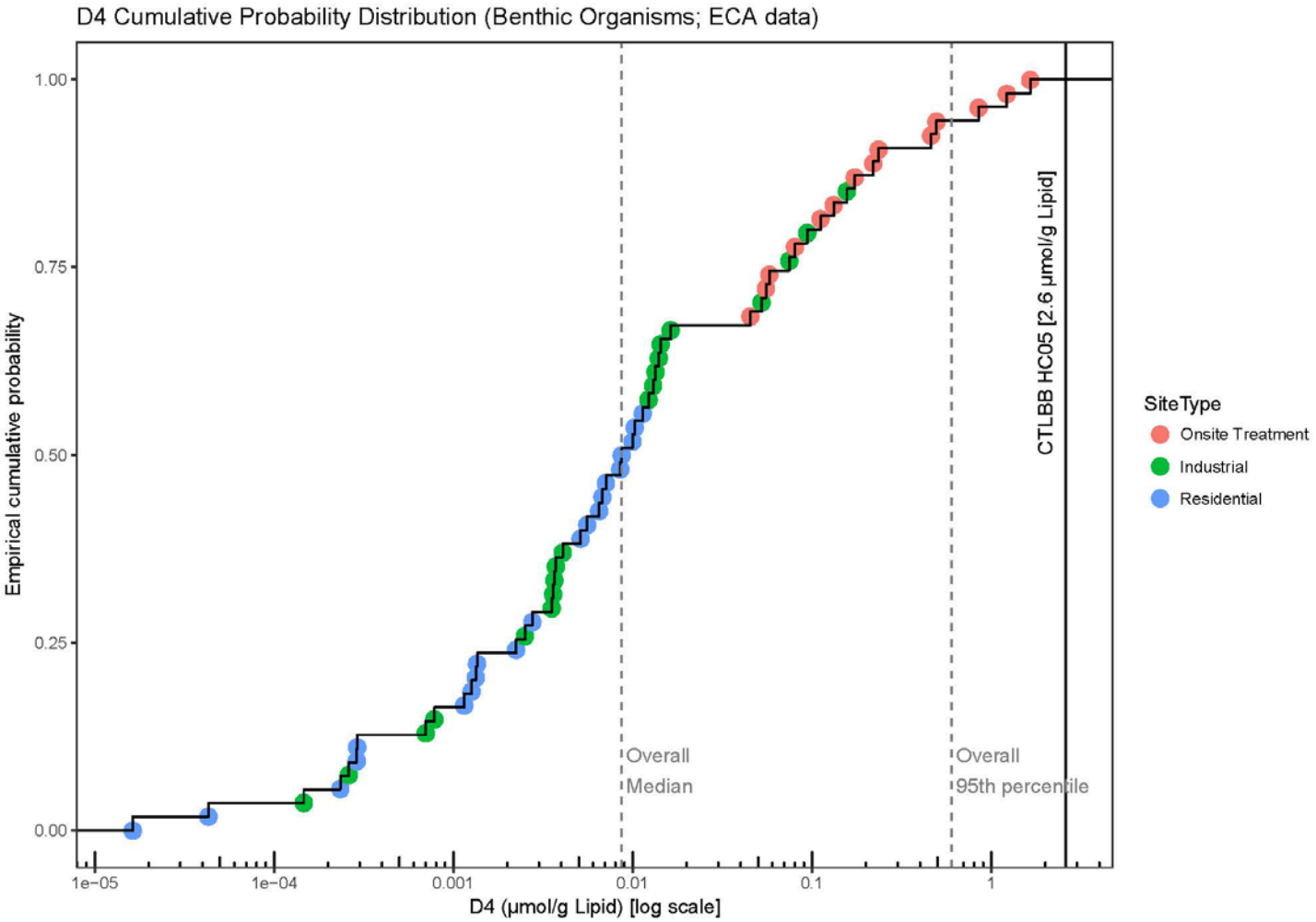


Figure 7-4. Comparison of lipid-normalized D4 concentrations in benthic invertebrate tissues to HC_5 critical tissue lipid body burden.

Note: The overall median and 95th percentile presented are for all three site types combined.

7.2.4 LoE 3: Activity Assessment

The third LoE compares chemical activity, calculated as described above, of D4 in water and sediment from environmental samples with activities calculated for the same media in prolonged-acute and chronic toxicity threshold tests (Figure 7-5). The calculated activity thresholds are shown in Table 7-5. D4 activities in water samples are compared to activity thresholds for aquatic invertebrates and fish since these thresholds were based on water exposure toxicity tests. D4 activities in sediment samples are compared to activity thresholds for benthic invertebrates since these thresholds were based on sediment exposure toxicity tests. D4 activities

in fish tissue samples are compared to activity thresholds for fish and D4 activities in benthic invertebrate tissue samples are compared to activity thresholds for benthic invertebrates. Activities of D4 in water from field samples were at least one order of magnitude less than the activity at the threshold concentration based on prolonged-acute toxicity in fish or the chronic toxicity test for water-column invertebrates and were seven times lower than the activity at the threshold concentration based on chronic toxicity in fish. With the exception of one sample collected downstream from MPF facility discharges, D4 activities in field sediment samples were below the activity in sediment at the threshold concentration based on prolonged-acute or chronic toxicity in benthic invertebrates. However, at all locations including this one, the D4 activities in benthic invertebrate tissue samples were below the activity thresholds for benthic invertebrates (Figure 7-5). None of the D4 activities in fish or benthic invertebrate tissue samples exceeded the thresholds for fish or benthic invertebrates. These results for D4 activities in fish and benthic invertebrate samples are in line with those for LoE 2, which showed that the tissue concentrations in fish and benthic invertebrates collected downstream of discharges of D4 were too low to cause toxicity via the narcosis MoA. These results are also in line with LoE 1, which showed no exceedances of the field surface water and sediment concentrations above the media-specific threshold concentrations.

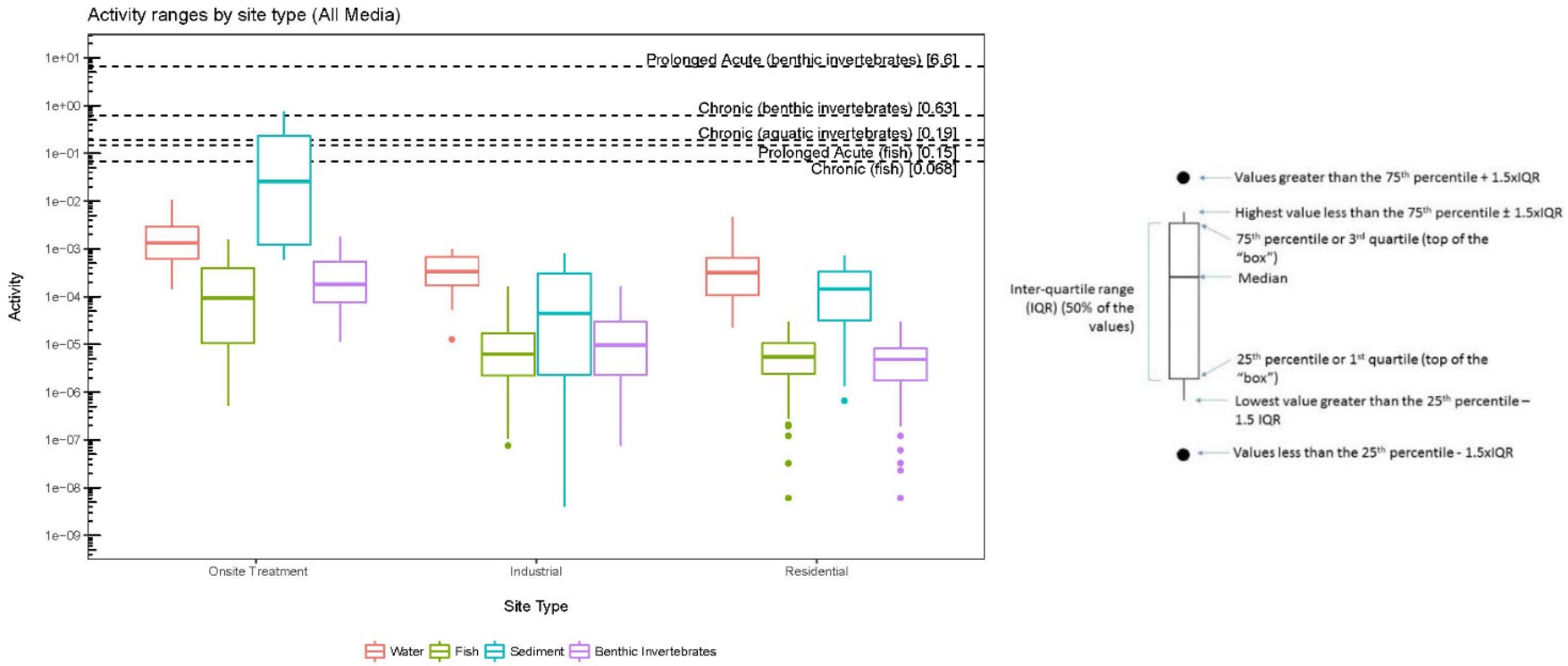


Figure 7-5. Comparison of D4 activities in environmental media to activities at toxicity thresholds.

Note: D4 activities in water samples are compared to activity thresholds for aquatic invertebrates and fish since these thresholds were based on water exposure toxicity tests. D4 activities in sediment samples are compared to activity thresholds for benthic invertebrates since these thresholds were based on sediment exposure toxicity tests. D4 activities in fish tissue samples are compared to activity thresholds for fish and D4 activities in benthic invertebrate tissue samples are compared to activity thresholds for benthic invertebrates.

7.2.5 LoE 4: Benthic Community Assessment Results

Several macroinvertebrate community and habitat metrics were used to examine possible relationships between D4 exposures and indigenous aquatic communities. Benthic metric (Table 7-6) show that while HBI tolerance values varied from poor to excellent, there does not appear to be a relationship with D4 concentrations (Figure 7-6.). For example, OT1 and OT2 had HBI tolerance scores of Very Good and Excellent for each of the sampling events, with a high percentage of the sensitive EPT species as compared to tolerant dipteran species (Table 7-6). Most of the sites on large rivers had lower benthic community scores and/or low taxa numbers, often the case for large rivers, where canopy cover, flow, and substrates are not optimal for taxa richness and sensitive benthic macroinvertebrates (e.g., many EPT species). This is compared to small high-gradient streams that often have good-to-excellent habitat. In general, the tolerance values were more closely related to habitat condition, where high-quality habitats have diverse benthic communities and low-quality habitats have more depauperate communities. Note, this trend was consistent at most locations across all three site types (on-site treatment, industrial, and residential), demonstrating habitat condition was likely the controlling variable in benthic community quality, not chemical exposures.

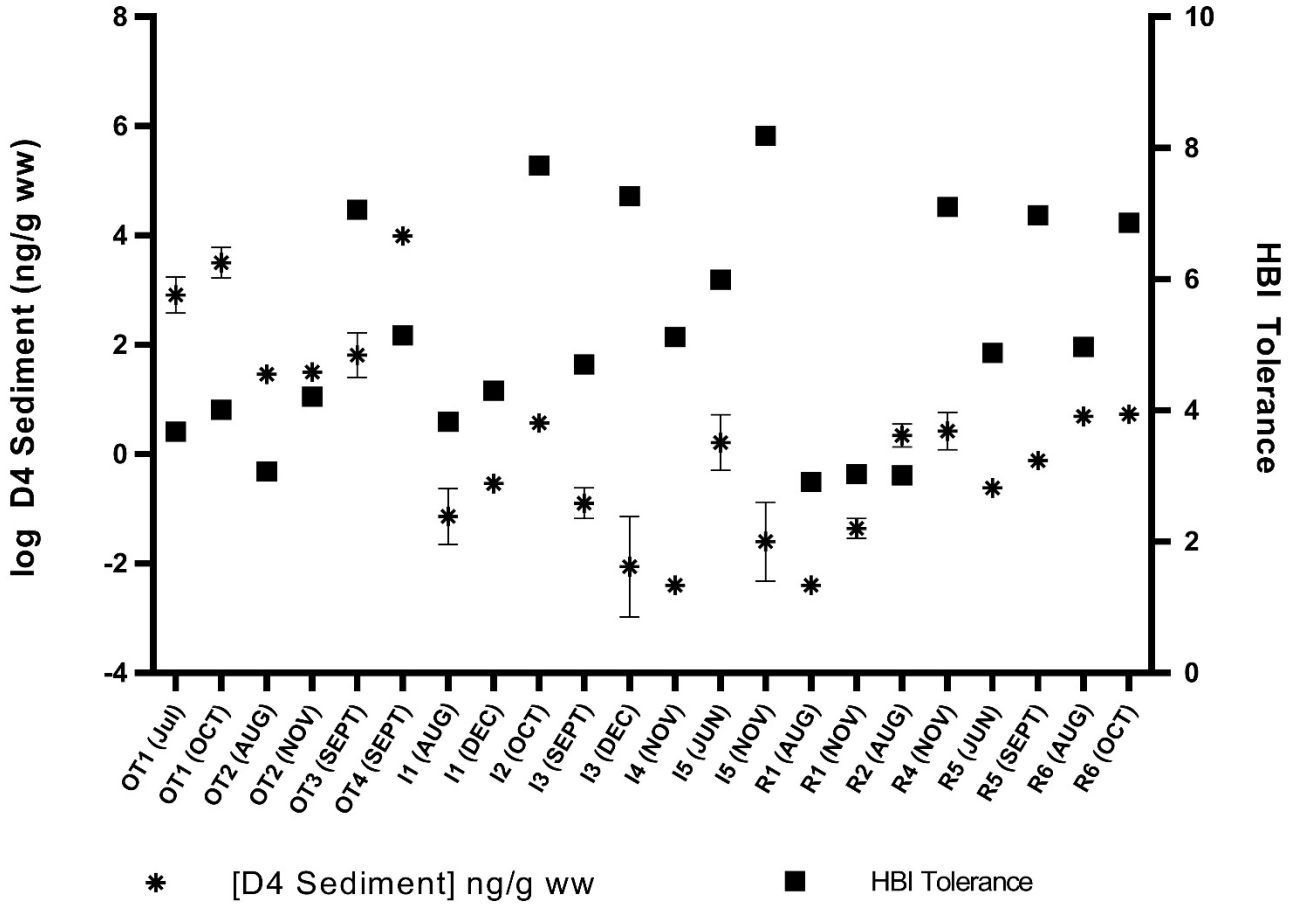


Figure 7-6. D4 concentrations in sediment (±SE) (grey bars) compared to HBI tolerance scores (black diamonds) are presented for each site and event where n>100 organisms.

Note: HBI Tolerance Scoring Evaluation: 0–3.75 = Excellent, 3.76–4.25 = Very Good, 4.26–5 = Good, 5.01–5.75 = Fair, 5.76–6.50 = Fairly Poor, 6.51–7.25 = Poor, 7.26–10.00 = Very Poor.

Table 7-6. Macroinvertebrate community and habitat metrics, presented for each site and event where n > 100 organisms

Site ID	Event	HBI	Water Quality based on HBI[a]	Habitat Metric Index[b]	# Taxa	# EPT Taxa	% EPT	% Dipteran
OT1	1	3.68	Excellent	Excellent	17	5	81.4%	1.5%
OT1	2	4.01	Very good	Excellent	16	4	76.1%	4.1%
OT2	1	3.07	Excellent	Fair	4	1	65.0%	0.0%
OT2	2	4.21	Very good	Fair	8	2	25.7%	27.9%
OT3	1	1.58	Excellent	Poor	3	1	15.8%	0.0%
OT3	2	7.06	Poor	Poor	9	1	6.5%	0.4%
OT4	1	5.73	Fair	Poor	3	1	6.5%	87.1%
OT4	2	5.14	Fair	Poor	12	1	0.6%	34.0%
I1	1	3.83	Very good	Fair	10	4	98.0%	0.3%
I1	2	4.31	Good	Poor	8	2	93.0%	0.0%
I2	1	6.04	Fairly poor	Fair	5	0	0.0%	67.9%
I2	2	7.74	Very poor	Fair	9	0	0.0%	33.1%
I3	1	4.71	Good	Poor	9	2	79.7%	0.0%
I3	2	7.27	Very poor	Fair	7	1	8.6%	13.0%
I4	1	4.40	Good	Fair	5	1	2.3%	11.6%
I4	2	5.12	Fair	Fair	6	1	0.1%	6.3%
I5	1	6.00	Fairly poor	Poor	7	0	0.0%	4.3%
I5	2	8.19	Very poor	Poor	5	0	0.0%	1.9%
R1	1	2.91	Excellent	Excellent	8	3	93.2%	3.6%
R1	2	3.03	Excellent	Good	10	5	88.2%	0.0%
R2	1	4.74	Good	Excellent	4	1	35.2%	40.9%
R2	2	3.01	Excellent	Excellent	7	3	74.8%	7.1%
R4	1	8.43	Very poor	Fair	5	0	0.0%	19.0%
R4	2	7.11	Poor	Fair	6	1	1.1%	57.4%
R5	1	4.88	Good	Good	15	4	24.8%	24.6%
R5	2	6.98	Poor	Good	18	2	13.9%	2.0%
R6	1	4.97	Good	Fair	8	2	73.4%	0.0%
R6	2	6.86	Poor	Fair	10	2	22.1%	0.8%

Notes:

[a] Modified Hilsenhoff Biotic Index values were calculated using the species and tolerance values from Mandaville (2002).

[b] Qualtitative habitat assessment scores were derived based on the substrate, cover, and morphology data obtained from field notes and site photographs.

7.2.6 LoE 5: Evaluation of Bioaccumulation Potential

Although concentrations of D4 were determined in multiple environmental matrices (i.e., water, sediment, and biota), the field data collected under the ECA program are inappropriate for developing bioaccumulation metrics. The study design did not account for spatial heterogeneity and temporal variability, nor was it designed to account for specific predator-prey trophic interactions, species migrations, and organism home ranges (Burkhard 2003; Gustavson et al. 2011; Borgå et al. 2012b; Mackay et al. 2015) or other ecosystem-specific factors such as sediment-water disequilibrium conditions (Gobas and MacLean 2003; Mackay et al. 2015). Additionally, there was limited statistical power at each site to compare media. Sufficient statistical power in terms of number of species and sites sampled is an important factor for appropriate design of a field bioaccumulation study (Conder et al. 2012; Burkhard et al. 2012; Gobas et al. 2015a). Therefore, no attempt was made to calculate BAFs, BSAFs, BMFs, or TMFs for the results obtained from the ECA monitoring study.

However, chemical activities calculated from measured environmental concentrations and physical/chemical parameters were compared across media (sediment, water, benthic invertebrates, and fish) to examine the tendency of D4 to partition into these different environmental media.

Comparing ranges of D4 activity across the various environmental media indicated a general decreasing tendency for D4 saturation from water and sediment to biota and from benthic invertebrates to fish (Figure 7-6 and Table 7-5). While this is not a direct measure of bioaccumulation potential, it provides insight into the relationships between meaningful bioaccumulation parameters. Additionally, this finding is in agreement with studies of D4, which have shown trophic dilution across food webs (Powell and Woodburn 2009; Powell et al. 2010, 2017, 2018; Borgå et al. 2013; McGoldrick et al. 2014a; Krogseth et al. 2017;) with only a few showing trophic magnification in select food webs (e.g., McGoldrick et al. 2014a). McGoldrick et al. (2014a) observed trophic dilution in 4 of the 5 Lake Erie food webs they investigated and trophic magnification in only one food web. The authors suggested that this could have been due to the inclusion/exclusion of different organisms occupying the highest and lowest trophic levels. While bioaccumulation metrics frequently have been used with persistent

organic pollutants such as polychlorinated biphenyls (PCBs) to predict the tendency of chemicals to bioaccumulate and biomagnify, cyclic siloxanes like D4 may not be amenable to the same predictive approaches. Gobas et al. (2015a) described how the predicted thermodynamic equilibrium BSAF between concentrations in sediment and benthic invertebrates for PCBs is approximately three (because for PCBs, the sorptive capacity of organic carbon (OC) is ~35% that of octanol [a surrogate for lipids]) and the magnitude of observed BSAFs is often around this number (Morrison et al. 1996; Wong et al. 2001). Thus, for PCBs, the predicted equilibrium between sediments and tissues is aligned with measured BSAFs. For D4 the sorptive difference is much greater. D4 is 186 to 575 times more soluble in octanol than OC ($K_{ow}=10^{(6.49–6.98)}$; $K_{oc}=10^{4.22}$). This implies a thermodynamic equilibrium between sediment and organisms is achieved when the BSAF reaches 186 (up to 575). However, field based BSAFs for D4 are significantly lower (e.g., *Lumbriculus variegatus*: BSAF = 6.7–19.7; Wildlife International, Ltd. 2008c), which may be partially attributed to biotransformation processes (Gobas et al. 2015a). Furthermore, it is difficult to evaluate bioaccumulation in the context of risk evaluation for superhydrophobic chemicals (those chemicals whose Log_{10} octanol water partition coefficient approaches or exceeds 7; Bruggeman et al. 1984; Mackay et al. 2015), because they often fail to meet the assumption of steady state partitioning. Given the continual, but fluctuating input of D4 into the environment from dischargers, along with its high volatility from the receiving water, it is likely D4 does not reach steady state in natural environments.

7.2.7 Weight-of-Evidence

A national-scale monitoring program (ECA) was conducted that measured D4 concentrations in relevant environmental matrices. The results of that program are used in conjunction with a multiple LoE approach to assess the potential for risks to freshwater aquatic and benthic communities from D4 discharged to receiving waters in rivers and streams from MPF facilities following on-site treatment or through municipal WWTPs. Concentrations in water, sediment, and biota downstream of discharges from municipal WWTPs and MPFs with on-site treatment were below toxicity threshold values derived from laboratory toxicity tests or from the HC5 CTLBB. Chemical activities in water also were at least seven times lower than the activity expected at toxicity threshold concentrations. Except for one sample, chemical activity in

sediment collected downstream of an MPF facility that discharged effluent after on-site treatment did not exceed toxicity threshold activities for benthic invertebrates. In the one elevated sample, the tissue concentrations measured in benthic invertebrates associated with this sampling location did not exceed the HC5 CTLBB threshold. This is in line with the previous findings that the tissue concentrations in aquatic organisms collected downstream of WWTP discharges of D4 were too low to cause toxicity via the narcosis MoA. Additionally, the comparison of sediment concentration to benthic toxicity thresholds did not indicate effects, and assessment of the benthic community showed no clear chemical-related effects. In terms of bioaccumulation potential, D4 is not expected to bioaccumulate and some data indicate it exhibits trophic dilution. Thus, all LoEs are in agreement, providing strong evidence of no unreasonable risks to ecological receptors from D4 discharged to rivers and streams in the United States, at the sites examined, under present-day emission levels.

Using multiple LoEs in a weight-of-evidence approach is one of the more reliable environmental risk evaluation tools to support decision-makers who must determine both the extent of pollution and its ecological significance (Burton et al. 2002; Linkov et al. 2009; Lotufo et al. 2014; Suter et al. 2017) and is central to the recommendations made by EPA for conducting risk evaluations under TSCA (U.S. EPA 2017a). By assembling a full inventory of the environmental data collected from 14 sites across the U.S. (two sampling events per site), including information on the benthic communities, the monitoring program provided information for a robust analysis of potential ecological risks of D4 discharges. It is acknowledged that the current evaluation assessed risks to aquatic receptors only from D4. As with any chemical-specific risk assessment, the potential influences of other chemical or non-chemical stressors remain uncertain. However, the findings reflect that existing management strategies for controlling the environmental releases of D4 are effective at maintaining environmental concentrations in receiving water bodies below concentrations that would be anticipated to cause adverse environmental impacts.

7.2.8 Uncertainty

Using multiple LoEs is a reliable approach to assessing risk to ecological receptors. However, each LoE has its own unique strengths and limitations; therefore, using multiple LoEs reduces

uncertainties associated with risk predictions. Although concentrations of D4 were determined in multiple environmental matrices (i.e., water, sediment, and biota), the field data collected under the ECA program are inappropriate for developing bioaccumulation metrics because the study design did not account for spatial heterogeneity and temporal variability, nor was the study designed to account for other factors such as specific predator-prey trophic interactions, species migrations, organism home ranges (Burkhard 2003; Gustavson et al. 2011; Borgå et al. 2012b; Mackay et al. 2015; Kim et al. 2016), and other ecosystem-specific factors such as sediment-water disequilibrium conditions (Gobas and MacLean 2003; Mackay et al. 2015).

Furthermore, there was limited statistical power at each sampling site to compare D4 concentrations in various media. Adequate statistical power in terms of number of species and sites sampled is important for appropriate design for a field bioaccumulation study (Conder et al. 2012; Burkhard et al. 2012; Gobas et al. 2015a). Therefore, BAFs, BSAFs, BMFs, or TMFs were not determined based on the data obtained from the ECA monitoring study. However, chemical activities calculated from measured environmental concentrations and physical/chemical parameters were compared across media (sediment, water, benthic invertebrates, and fish) to examine the tendency of D4 to partition into these different environmental media.

The ECA monitoring program, with sites selected to be representative of the approximately 15,000 to 20,000 municipal WWTPs in the continental United States as well as industrial discharge sites, was designed to represent worst-case exposures of biota to D4 in receiving streams and rivers downstream of dischargers. Samples were collected from within the mixing zones of these waters and during periods of low flow. Mixing zones compose only a small area of the receiving water ecosystem, and dilution occurs immediately downstream of the zone; sampling under low-flow conditions ensured that concentrations of discharged chemicals would be at their highest levels for the year. The findings from the ECA monitoring study are consistent with results from Woodburn et al. (2018), who compiled field concentrations of cVMSs (including D4) from previous monitoring studies conducted in 2001–2015 in sediments from urban waterways, downstream from municipal and industrial WWTPs, landfills, large freshwater lakes, and marine systems. The highest sediment concentrations were associated with urban settings and industrial WWTPs, which were comparable to concentrations in the ECA

monitoring study. Samples were collected under various flow conditions and distances from potential sources and, as in the ECA study, the 95th percentile of the measured concentrations of D4 in sediment did not overlap with benthic invertebrate toxicity thresholds.

While the ECA was a comprehensive survey, the survey design was not probabilistic, which introduces some uncertainties when extrapolating to a national scale. Indigenous fish and benthic communities were sampled at a wide range of sites, exhibiting a range of dilutions (Table 5-21). Their biological responses should capture the temporal variability that affects D4 exposures. Assessing effects to benthic organisms is particularly important in assessing risks to freshwater ecosystems. Benthic communities are important for ecosystem quality because they are a key component in processing and cycling organic matter, affecting key biogeochemical cycles such as those for nitrogen, phosphorus and sulfur, and serving as a food source for fish and higher trophic level organisms. While benthic organisms tend to be sedentary in nature, they also drift from upstream or are washed downstream during high-flow events. If sediments are contaminated, sensitive benthic species will continue to drift downstream until suitable sediments are found for colonization. This suggests that benthic species found at a site are reflective of suitable habitat conditions. The benthic community is potentially impaired by a multiplicity of stressors, particularly in human-dominated watersheds (Burton and Johnston 2010). These include habitat-related stressors, such as altered flow, sedimentation and depositional sediments, and temperature. Other stressors common to altered landscapes are elevated nutrients, low dissolved oxygen, pesticides, pharmaceuticals, and personal care products. It is very difficult to assign causality between an impaired benthic community and any single stressor in a watershed. However, when poor benthic habitat exists, it is possible to conclude that habitat will be the dominant stressor, and when high-quality benthic communities are present in high-quality habitat, it is reasonable to conclude that other factors are not significant stressors.

Benthic community metrics ranged from excellent to poor (Table 7-6) and did not correlate to D4 sediment concentrations (e.g., even sites receiving discharge from MPF facilities after on-site treatment had high-quality HBI tolerance scores) (Figure 7-6.). This study also showed the importance of pairing habitat assessments with the benthic macroinvertebrate community

surveys in understanding where the benthic macroinvertebrate community may be self-limited by background watershed and habitat conditions or by impacts from current land uses, thus correctly apportioning community degradation to chemical impacts or other factors. Indeed, the benthic metrics matched closely with habitat quality (Table 7-6), and poorer habitat conditions resulted in tolerant, less diverse benthic communities more typical of a habitat-degraded stream.

The risk characterization approach employed herein moves beyond the standard deterministic hazard quotient approach towards a probabilistic risk assessment (PRA) that incorporates more advanced methods for risk prediction using distributions rather than conservative point estimates of exposure to explicitly account for variability and uncertainty in the ecological system being assessed. It clearly demonstrates that monitoring data collected to characterize emissions of D4 support EPA's stated intent to “strive to utilize probabilistic approaches for exposure assessments included in a risk evaluation” (U.S. EPA 2017b) during TSCA mandated chemical reviews. Variability refers to inherent natural variation across time and space in environmental attributes (either biotic or abiotic) and the precision and accuracy of measurements, while uncertainty refers to imperfect knowledge about the system being studied. Deterministic assessments account for variability and uncertainty using highly conservative point estimates for exposure and the application of assessment factors (AFs) on effect concentrations observed for the most sensitive species. This results in hazard indices based on scenarios highly unlikely to occur in the environment (Hope 2012). The result is a highly protective but not very realistic risk estimate. PRA, on the other hand, explicitly incorporates uncertainty and variability into the risk assessment, resulting in a realistic and quantifiable probability of an adverse outcome (U.S. EPA 2014). Coupled with a multiple-LoEs approach such as used in this evaluation of risks of D4, this affords the risk manager a broad base of information upon which to base a decision. Thus, a standard deterministic risk assessment might ascribe risk to fish and sediment organisms downstream of MPFs that discharge through on-site wastewater treatment (i.e., the highest measured environmental exposure concentrations exceed the lowest AF-adjusted toxicity thresholds). However, the fish chronic threshold is based on an unbounded NOEC, (i.e., no effects were observed at the highest test concentration); thus, the true threshold may actually be above the conservatively selected threshold used. Additional reasoning for the inappropriateness of applying AFs for this D4 risk evaluation are discussed subsequently.

The use of AFs in a risk assessment significantly lowers the toxicity threshold values. It is intended to account for the uncertainty in laboratory tests and extrapolation to untested species, although it has been argued that AFs are arbitrary and nontransparent (Chapman et al. 1988; Fairbrother 2010). Furthermore, for difficult-to-test substances such as D4, which have high volatility and low water solubility, toxicity tests are often performed with artificially closed systems with high concentrations of stock solutions forcing the chemical into solution at high concentrations under conditions that do not reflect environmentally realistic conditions (OECD 2002) and are thus already conservative in nature. Given that toxicity thresholds for D4 are at or near maximum functional solubility in all the laboratory tests, this argues against the application of AFs to artificially decrease the threshold concentration for toxic effects. Additionally, although the toxicity dataset only provides a few species representing each trophic level, D4 exhibits toxicity via the well understood MoA of narcosis or baseline toxicity, and the tissue concentrations of D4 measured in all fish and benthic invertebrate samples were all less than the CTLBB that is protective of 95% of species. The results from the use of a LoE approach where multiple LoEs are in agreement support a conclusion that there is no unreasonable risk to the freshwater ecosystem from D4. Thus, it is clear that, in the case of D4, a conventional deterministic risk assessment approach including the application of AFs is inappropriate and would implement overly conservative assumptions, resulting in an overestimate of risks to ecological receptors from environmental releases of D4.

7.2.9 Summary of Ecological Risk Characterization

A nation-wide environmental D4 monitoring study of discharges from municipal WWTPs and MPFs with on-site WWTP to the freshwater receiving environment provided high-quality data for conducting a realistic ecological risk characterization. Using multiple LoEs, it is evident that there is no unreasonable risk from D4 to organisms based on environmentally realistic exposure concentrations, likely due in part to the volatility and hydrolysis of D4 and the ability of organisms to biotransform and excrete the chemical (Gobas et al. 2015a). The monitoring study collected samples from within the mixing zones at the discharge sites, which compose only a small area of the receiving water ecosystem, and under low-flow conditions. Therefore, the study represents conservative exposures to biota, and thereby resulted in a conservative risk evaluation.

8 Risk Determination

In the risk determination step, a conclusion is reached regarding whether a chemical substance presents an unreasonable risk of injury to health or the environment, under the conditions of use. The determination does not consider costs or other non-risk factors. As described by EPA TSCA, the risk-relevant factors to be considered include, but are not limited to: "the effects of the chemical substance on health and human exposure to such substance under the conditions of use (including cancer and non-cancer risks); the effects of the chemical substance on the environment and environmental exposure under the conditions of use; the population exposed (including any susceptible populations), the severity of hazard ([including] the nature of the hazard, the irreversibility of hazard), and uncertainties." The confidence in the data used in the risk estimate should be considered, including the strengths, limitations and uncertainties associated with the information used to inform the risk estimate and the risk characterization. This approach is in keeping with the Final Rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726).

Under TSCA, conditions of use are defined as the circumstances under which the substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of. An unreasonable risk may be indicated where the health risks or environmental risks under the conditions of use are greater than the risk benchmarks. The degree of uncertainty surrounding these indications is a factor in determining whether or not unreasonable risk is present. The nature of the potential effects, the degree of the potential exposure, and the protectiveness of the assumptions are also factors.

8.1 Risks to Human Health

8.1.1 Determining Non-Cancer Risks

MOEs are a widely recognized point estimate method for evaluating potential non-cancer health risks from exposure to a chemical. As described in Section 7.1.3, the MOE is the POD for a specific health endpoint divided by the exposure concentration for the specific scenario of concern. For D4, BMD modeling of the results from a two-generation inhalation reproduction

study in rats was used to determine a POD. PBPK modeling was executed with human parameter values for both physiological parameters and for D4-specific parameters to develop estimated internal dose-metrics that were unique to the receptor, route of exposure, and exposure pattern. The NOAEC was 300 ppm, however the more conservative BMDL endpoint of 125 ppm based on BMD was the basis for the POD. The POD for all populations (including children), durations, and routes of exposure was 30 mg-hr/L blood/day, based on the AUC of free D4 in the blood and on the worst-case assumption of continuous exposure.

Exposures were assessed for workers, consumers, and the general population. For workers, an assessment based on skin care product formulators which are not TSCA relevant, was found to be the worst case for all TSCA-relevant worker exposures. The exposure assessments for consumers and the general population also included non-TSCA relevant exposures to personal care products, cosmetics, OTC medication, and food contact materials. These approaches provided additional conservatism to the assessment.

The benchmark MOE was 100, based on a 10X for intra-human variability, 1X for extrapolation from animal-to-human (based on the use of PBPK data), and 10X for remaining sources of uncertainty related to the database. This latter 10X uncertainty factor accounts for the current PBPK model (McMullin et al. 2016) which is not designed to estimate internal dose metrics for children or pregnant/lactating women. Therefore, these potentially exposed or susceptible subpopulations were addressed through the use of this conservative benchmark MOE.

All calculated MOEs were well above the benchmark MOE of 100, indicating no unreasonable risk to human health. The approach used includes conservative assumptions in the selection of the POD and the inclusion of exposures from non-TSCA related uses, and thus affords a wide margin of certainty. The highest risk (lowest MOE) was 15,000 for inhalation exposure of male workers in the formulation of skin care products (surrogate for TSCA-relevant uses). Risks to consumers are an order of magnitude less than for workers, and risks to the general population are another order of magnitude less than those for consumers (noting that exposures to consumers and the general population also included non-TSCA relevant uses). Aggregate risks were comparable to those for skin care formulators, with the aggregate MOEs two orders of magnitude above the benchmark MOE.

8.1.2 Determining Cancer Risks

D4 has not been identified as having cancer effects. Therefore, risk estimates for cancer were not included in this risk evaluation.

8.2 Environmental Risk

The approach used in the environmental risk characterization moved beyond a risk quotient approach to incorporate multiple lines of evidence (LoE) and probabilistic assessment of exposure. Five LoEs were gathered and used in a weight-of-evidence approach. The LoEs include 1) comparing D4 concentrations measured in environmental media to toxicity thresholds derived from laboratory bioassays with sensitive organisms; 2) comparing D4 concentrations measured in biota tissue to the CTLBB derived from the TLM; 3) fugacity-based chemical activity assessment; and 4) assessing benthic community metrics. A fifth LoE assessment is the consideration of bioaccumulation potential.

Data from guideline and non-guideline sponsor-owned studies and literature studies were evaluated for the effects assessment. Thresholds of toxicity to water column and sediment organisms were developed based on these data, a metric of critical body residues of D4 was established using a TLM assessment, and chemical activity was calculated at toxicity threshold concentrations. The exposure assessment was based on the results of a national-scale monitoring program that measured D4 concentrations in relevant environmental matrices downstream from MPF facilities with on-site treatment, municipal WWTPs receiving industrial discharges (e.g., D4 reasonably expected in the influent), and municipal WWTPs that did not receive industrial discharges. Cumulative distributions of concentrations of D4 measured in water and sediment samples for each site type, as well as overall medians and 95th percentiles of the data for all three site types combined, indicated no exceedances of toxicity thresholds (LoE 1).

In the second LoE, cumulative distributions of lipid normalized tissue concentrations of D4 measured in field-collected fish and benthic organisms were compared to the tissue concentration below which no narcosis effects would be expected for 95% of aquatic organisms (HC5 CTLBB). No D4 concentrations in fish or benthic invertebrate tissue exceeded the HC5

CTLBB, signifying that the tissue concentrations in aquatic organisms collected downstream of municipal WWTP discharges and discharges of D4 from on-site treatment sites were too low to cause toxicity. The third LoE compared chemical activity of D4 in water, sediment, and tissue samples collected during the monitoring program with activities calculated for the same media or organism type in prolonged-acute and chronic toxicity threshold tests. The findings from this LoE further support the conclusions of the first two LoEs. The fourth LoE, benthic community assessment, indicated there was no relationship between D4 exposures and measures of benthic community health. In terms of bioaccumulation potential, D4 is not expected to bioaccumulate and data indicating it exhibits trophic dilution. Thus, all LoEs are in agreement, providing strong evidence of no unreasonable risks to ecological receptors from D4 discharged to rivers and streams in the United States, at the sites examined, under present-day emission levels.

The PRA approach, as used in the environmental risk characterization for D4, explicitly incorporates uncertainty and variability into the risk assessment, resulting in a realistic and quantifiable probability of an adverse outcome (U.S. EPA 2014). Coupled with a multiple-LoEs approach such as used in this evaluation, a robust information base is provided and uncertainty is minimal. Moreover, the ECA monitoring program was designed to represent worst-case exposures of biota to D4 in receiving streams and rivers downstream of D4 dischargers. Samples were collected from within the mixing zones of these waters and during periods of low flow to provide the highest estimates of exposure. The resulting conclusions of no unreasonable risk, based on the weight-of-evidence, support a determination of no unreasonable risk to the environment from D4 under the conditions of use being evaluated.

8.3 Risk Determination for D4

D4 does not present unreasonable risk of injury to human health or the environment under the conditions of use. Risks to workers, consumers, the general population (including potentially exposed or susceptible subpopulations), and the environment from D4 were evaluated and found to present no unreasonable risk. This risk determination is summarized below and in Table 8-1.

Human Health

- Workers: This evaluation found no unreasonable risk to the health of workers from the conditions of use for D4, including TSCA-relevant occupational exposures, and non-TSCA relevant exposures (formulation of personal care products, office workers, and barbers and beauticians). For all conditions of use, inhalation exposure scenarios resulted in calculated MOEs that did not indicate unreasonable risk relative to the respective benchmark.

- Consumers: This evaluation found no unreasonable risk to the health of consumers (for all populations (adults, children, and pregnant/lactating females). The evaluation was based on conservative non-TSCA relevant exposure to D4 in personal care products and concluded, for all conditions of use, exposure scenarios resulted in calculated MOEs that did not indicate unreasonable risk relative to the respective benchmark.

- General Population: This evaluation found no unreasonable risk to the health of the general population (adults, children, pregnant/lactating females, and substitence fisherman). All exposure scenarios resulted in calculated MOEs that did not indicate risk relative to the respective benchmark.

- Sentinel risk assessment found no unreasonable risk based on estimating the sentinel exposure (skin care product formulators), which results in MOEs at least 150-fold more than the benchmark MOE of 100. MOEs for consumers and the general public who may be exposed to D4 were even higher, similarly indicating D4 does not pose unreasonable risk to human health.

- Aggregate risk assessment (across worker, consumer, and the general population exposure pathways) found no unreasonable risk, with aggregate calculated MOEs at least 120-fold more than the benchmark MOE of 100.

Ecological

Using a nation-wide monitoring dataset for D4 (the ECA monitoring program), which represents conservative exposures of biota to D4 in receiving streams and rivers downstream of D4 dischargers, and a weight of evidence from five LoE, the ecological risk assessment reached a conclusion of no unreasonable risk of injury to the environment.

Disposal

Because D4 is a valuable product and not a waste substance, emissions to air, land, and water from MPF facilities are minimized. These emissions are handled in accordance with local, state and federal regulations. Air emissions are managed through engineering controls and pollution control equipment (such as scrubbers, condensers, or energy recovery systems). Liquid waste is treated through either on-site treatment or discharge to a municipal WWTP (either with or without pre-treatment) for further treatment. The sludge produced from wastewater treatment is disposed of at on-site landfills or shipped to off-site management systems. These management systems may include incinertors, energy recovery systems or other beneficial use (excluding use as fertilizer), or landfills. Solid waste is subject to fuel recovery or off-site waste management. Further detail is provided in Section 4.1.5.

Table 8-1. Health and environmental risk determination

Life Cycle Stage	Category [a]	Subcategory [b]	Risk Determination
Manufacture	Domestic Manufacture	Domestic Manufacture	D4 does not represent an unreasonable risk of injury to health (workers, consumers, and the general population) or the environment (aquatic and benthic organisms). Human health exposure scenario with the highest risk estimate: noncancer effects from inhalation exposure of male workers in the formulation of skin care products (surrogate for manufacturing exposure for TSCA-relevant uses) Benchmark: MOE = 100 Risk estimate: MOE = 15,000 (see Table 7-1) Environment exposure scenario with the highest risk estimate: Overall 95th percentile for surface water (see Figure 7-1), sediment (see Figure 7-2), fish tissue (see Figure 7-3), benthic invertebrate tissue (see Figure 7-4) Environmental risk driver benchmark: prolonged acute and chronic values for fish and benthic invertebrates (see Table 7-5) and HC5 CLTBB (2.6 µg/mol lipid). Environmental risk estimates: exposures below thresholds for surface water, sediment and tissue (see Figures cited above). Supported by other LoEs including activity assessment (Figure 7-5) and benthic community assessment (Figure 7-6) and Table 7-6. Systematic Review confidence rating (health hazard): High Systematic Review confidence rating (health exposure): High Systematic Review confidence rating (environmental hazard): High Systematic Review confidence rating (environmental exposure): High Risk considerations: For human health, all MOE estimates for the most highly exposed groups are not below the conservative benchmark. Therefore, D4 does not pose an unreasonable risk to human health. This evaluation includes non-TSCA relevant uses and other conservative assumptions. For the environment, the results of multiple lines of evidence, including those derived from an extensive monitoring program, indicate risks are below thresholds and therefore, not unreasonable.
Processing	Processing as a reactant	All Other Basic Organic Chemical Manufacturing	
		Other Basic Organic Chemical Manufacturing	
		All Other Basic Inorganic Chemical Manufacturing	
		All Other Chemical Product and Preparation Manufacturing	
		Resin and Synthetic Rubber Manufacturing	
		Synthetic Rubber Manufacturing	
		Adhesive manufacturing	
	Processing-incorporation into formulation, mixture, or reaction product	Paint and Coating Manufacturing	
		All Other Basic Inorganic Chemical Manufacturing	
		All Other Chemical Product and Preparation Manufacturing	
		Miscellaneous Manufacturing	
Commercial/Consumer Use	Adhesives and sealants		

Life Cycle Stage	Category [a]	Subcategory [b]	Risk Determination
	Automotive care products Cleaning and furnishing care products Paints and Coatings *Personal care products*[c] Plastic and Rubber Products not covered elsewhere Polishes and sanitation goods Rubber and plastic products Soaps and detergents		D4 does not represent an unreasonable risk of injury to health (workers, consumers, and the general population) or the environment (aquatic and benthic organisms). Human health exposure scenario with the highest risk estimate: noncancer effects from dermal exposures of female users of hand/body lotion (surrogate for consumer exposure for TSCA-relevant uses). Benchmark: MOE = 100 Risk estimate: MOE = 95,000 (see Table 7-2) Environment exposure scenario with the highest risk estimate: Overall 95th percentile for surface water (see Figure 7-1), sediment (see Figure 7-2), fish tissue (see Figure 7-3), benthic invertebrate tissue (see Figure 7-4) Environmental risk driver benchmark: prolonged acute and chronic values for fish and benthic invertebrates (see Table 7-5) and HC5 CLTBB (2.6 µg/mol lipid). Environmental risk estimates: exposures below thresholds for surface water, sediment and tissue (see Figures cited above). Supported by other LoEs including activity assessment (Figure 7-5) and benthic community assessment (Figure 7-6 and Table 7-6). Systematic Review confidence rating (health hazard): High Systematic Review confidence rating (health exposure): High Systematic Review confidence rating (environmental hazard): High Systematic Review confidence rating (environmental exposure): High Risk considerations: For human health, all MOE estimates for the most highly exposed groups are not below the conservative benchmark. Therefore, D4 does not pose an unreasonable risk to human health. This evaluation includes non-TSCA relevant uses and other conservative assumptions. For the environment, the results of multiple lines of evidence, including those derived from an extensive monitoring program, indicate risks are below thresholds and therefore, not unreasonable.

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Appendix A

Systematic Review Protocol

Systematic Review Protocol - Risk Evaluation of D4

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Introduction

The Toxic Substances Control Act (TSCA) requires that the U.S. Environmental Protection Agency (EPA) use data and information in a manner consistent with the best available science[1] and that decisions are based on the weight of the scientific evidence.[2] The final rule Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act, 82 FR 33726 (July 20, 2017) provides definitions for "best available science" and "weight of scientific evidence" as detailed in the footnotes below.

To meet the TSCA science standards, EPA's Office of Pollution Prevention and Toxics (OPPT) has indicated it intends to apply systematic review principles in the development of risk evaluations (page 9, U.S. EPA 2018). EPA strongly recommends that external parties use systematic review approaches when developing draft risk evaluations (page 12, U.S. EPA 2017a). Moreover, a protocol describing the process to be followed should be developed during the scoping/problem formulation phase of the risk evaluation to clearly state the procedures that will be used. Planning the systematic review approaches and methods in advance reduces the likelihood of introducing bias into the risk evaluation process.

The preamble to the final rule at 82 FR 33726 refers to the definition for systematic review given by the Institute of Medicine (National Academy of Sciences 2017): ''a scientific

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1 *Best available science* means science that is "reliable and unbiased." Use of best available science "involves the use of supporting studies conducted in accordance with sound and objective science practices, including, when available, peer-reviewed science and supporting studies and data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data). Additionally, EPA will consider as applicable (1) the extent to which the scientific information, technical procedures, measures, methods, protocols, methodologies, or models employed to generate the information are reasonable for and consistent with the intended use of the information; (2) the extent to which the information is relevant for the Administrator's use in making a decision about a chemical substance or mixture; (3) the degree of clarity and completeness with which the data, assumptions, methods, quality assurance, and analyses employed to generate the information are documented; (4) the extent to which the variability and uncertainty in the information, or in the procedures, measures, methods, protocols, methodologies, or models, are evaluated and characterized; and (5) the extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies, or models."

2 *Weight of the scientific evidence* means "a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study, and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance."

investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. The goal of systematic review methods is to ensure that the review is complete, unbiased, reproducible, and transparent.'' EPA has stated (U.S. EPA 2018) that the systematic review process should generate "high-quality, fit-for-purpose risk evaluations that rely on the best available science and the weight of the scientific evidence within the context of TSCA" and that the key elements of a systematic review include the following:

- A clearly stated set of objectives (defining the question)
- Developing a protocol that describes the specific criteria and approaches that will be used throughout the process
- Applying the search strategy in a literature search
- Selecting the relevant papers using predefined criteria
- Assessing the quality of the studies using predefined criteria
- Analyzing and synthesizing the data using the predefined methodology
- Interpreting the results and presenting a summary of findings.

This document provides the protocol that will be used for the systematic review of data and information as part of the preparation of a risk evaluation dossier for octamethylcyclotetrasiloxane (referred to hereafter as D4). The risk evaluation dossier, which is being prepared by Exponent on behalf of the Silicones Environmental, Safety, and Health Center (SEHSC) of the American Chemistry Council (ACC), will include a draft risk evaluation that is prepared consistent with EPA's *Guidance to Assist Interested Persons in Developing and Submitting Draft Risk Evaluations under the Toxic Substances Control Act* (U.S. EPA 2017a).

Objectives

The objectives of the systematic review are to gather, evaluate, and integrate data/information on D4 in the topic areas listed in Table 1 for use in exposure assessment, hazard assessment, and ultimately risk characterization. The topic areas and information needs are informed by conceptual site models (CSMs) that have been developed to describe exposure of humans and ecological receptors to D4.

Table 1. Information needed for D4 Risk Evaluation

Topic Area	Information Needs
Physical/Chemical Properties	• Collection of physico-chemical properties to inform the fate, exposure, and hazard assessments of the risk evaluation
Conditions of Use	• Known, intended, and reasonably foreseen conditions of use, including manufacturing, processing, distribution, industrial, commercial and consumer uses, and disposal
Fate	• Environmental mobility • Environmental degradation • Bioaccumulation and environmental persistence • Wastewater removal processes
Engineering and Exposure	• Lifecycle and process related information to inform worker, consumer and general population exposures • Environmental releases • Occupational exposure • Media concentrations in the environment • Biomonitoring data • Information to identify potentially exposed and susceptible subpopulations
Human Health Hazard	• Information about health hazards including critical health effects and corresponding points of departure, associated with exposure via all routes, durations, sources, and pathways • Characterization of exposure for general and potentially exposed and susceptible subpopulations • Toxicokinetics • Mode of action (MOA) • Information to identify potentially exposed and susceptible subpopulations
Environmental Hazard	• Information about environmental hazards associated with acute and chronic toxic effects on aquatic species, including both direct and indirect exposure (note: terrestrial species excluded from conceptual site models and the rationale for this will be provided in the risk evaluation)

EPA's guidance (U.S. EPA 2018) defines six activities in the systematic review process, each with a number of steps (e.g., development of screening categories, pilot testing, etc.). These activities include data search, data screening (title/abstract), data screening (full text), data extraction, data evaluation, and data integration. Iteration is a natural component of the process, and could be triggered by a variety of factors; therefore, this protocol may be modified based on initial findings.

Because existing data and information for D4 have been collated and evaluated in recent authoritative regulatory reviews by Canada and the United Kingdom (EC/HC 2008; Brooke et al. 2009), the systematic review for D4 will build off those results and focus primarily on information that has become available since 2008. In particular, the literature search will focus

on information since 2008, while the systematic review of information will not be constrained in this manner. The phases and steps of the review are summarized in Table 2. Each of these activities is described in more detail in the following sections.

Table 2. Phases and Steps of Systematic Review for D4 Risk Evaluation

Phase	Process Step
Data Search	
	Define specific objectives for the search
	Develop search strategies, including sources, search strings, date range or other filters
	Execute search, store results
	QA/QC
Data Screening (Title/Abstract)	
	Develop inclusion/exclusion criteria; refine as needed
	Conduct screening and document results
	QA/QC
Data Screening (Full Text)	
	Develop inclusion/exclusion criteria; refine as needed
	Conduct screening and document results
	QA/QC
Data Extraction	
	Develop templates to capture desired attributes
	Perform data extraction
	QA/QC
Data Evaluation	
	Develop criteria for evaluation and instructions for use
	Specify expertise of reviewers
	Evaluate and document study quality
	QA/QC
Data Integration	
	Develop strategy for analyzing and summarizing data/information across studies within each evidence stream, including strengths, limitations, and relevance.
	Develop strategy for weighing and integrating evidence across evidence streams, including strengths, limitations, and relevance.
	Conduct and document the analysis and synthesis of evidence; document the conclusions within each evidence stream.
	Weigh and document results across evidence streams to develop weight-of-evidence conclusions; document any professional judgment, including underlying assumptions.
	QA/QC

Data Search

The objectives for the search are listed by each topic area as information needs in Table 1. Common elements to the search strategy to be used for each topic area include the following:

- Search to contain CAS Registry Number (CASRN, 556-67-2) and/or chemical name (octamethylcyclotetrasiloxane), synonyms, trade names, and common misspellings.
- Search dates limited to 2008–present (due to the authoritative reviews done by the UK Environment Agency [Brooke et al. 2009] and Environment Canada/Health Canada [EC/HC 2008]).
- Information to be in English.

A preliminary screening assessment identified the availability of data for most, if not all, of the relevant physical/chemical properties, environmental fate properties, human health related effects, and ecological effects. Much of this data are from laboratory studies conducted by industry according to standard guidelines and under Good Laboratory Practices (GLP) regulations. Although Exponent is already in possession of the studies conducted by industry; a search of the TSCATS (Toxic Substances Control Act Submission Database) will be performed to cross-check against the studies provided by SEHSC.

In addition to the industry-sponsored studies, two main source categories of information are targeted for searching: the peer-reviewed literature and the gray literature/databases. Searches of the peer-reviewed literature will be conducted primarily using Google Scholar and Google or Bing search engines using the search terms described below for each topic area. For human health effects information (animal toxicity, *in vitro* toxicity, and epidemiological studies), PubMed will be used in addition to Google Scholar and Google or Bing search engines.

The gray literature[3] and government resources, including databases, will be explored by searching on the web sites listed in Appendix A (see Tables A1 and A2).

[3] *Gray literature* refers to sources of scientific information that are not formally published and distributed in peer-reviewed journal articles. These references are still valuable and consulted in the TSCA risk evaluation process. Examples of grey literature are theses and dissertations, technical reports, guideline studies, conference proceedings, publicly-available industry reports, unpublished industry data, trade association resources, and government reports

Relevant databases on the ProQuest DIALOG search service (Appendix B) and the American Chemical Society's STN® service (Appendix C) will also be searched. Some of the potentially relevant ProQuest databases include BIOSIS® Toxicology; CAB ABSTRACTS; Chemical Business NewsBase; Chemical Engineering & Biotechnology Abstracts; Chemical Safety NewsBase; Engineered Materials Abstracts; Environmental Engineering Abstracts; Gale Group Trade & Industry Database™; Material Safety Data Sheets - OHS™; NTIS; Pollution Abstracts; ProQuest Biological & Health Sciences Professional; ProQuest Environmental Science Professional; SciSearch; Toxfile®; and Water Resources Abstracts. Some of the potentially relevant STN databases include Chemical Abstracts; Regulated Chemicals Listing; Elsevier BIOBASE; Cosmetic & Perfume Science and Technology; and TOXCENTER. The search terms for use with these databases will be developed by Exponent Information Resources Department staff after consultation with a member of Exponent's D4 project team.

Search Strategy for Physical/Chemical Properties

A search for any new information in this topic area will be conducted using the ACS STN service. In addition to the previously mentioned terms and constraints, search terms will include the following: melting point, boiling point, vapor pressure, water solubility, octanol-water partition coefficient, and octanol-air partition coefficient.

Search Strategy for Conditions of Use

For this topic area, search terms will include synonyms, trade names, and common misspellings (in addition to CASRN and chemical name). A search of information reported to EPA will be performed to include Chemical Data Reporting (CDR)[4] and the Toxics Release Inventory (TRI).[5] To identify formulated products, EPA's Chemical and Product Categories (CPCat) data, the National Institute for Health's (NIH) Household Product Database, and any Safety Data Sheets (SDS) provided by SEHSC member companies will be reviewed. The list of products will be crosschecked, as necessary, with public data, publicly available literature, and trade

[4] https://www.epa.gov/chemical-data-reporting

[5] https://www.epa.gov/toxics-release-inventory-tri-program

publications to find known uses of D4. Other information sources as listed in Appendix A will also be used.

Search Strategy for Environmental Fate

Searches of the peer-reviewed literature, gray literature, and government resources will be conducted to identify any new information. The keywords will include the following:

> *CASRN, chemical name,* (*including synonyms, trade names, and common misspellings), absorption, adsorption, organic carbon-water partition coefficient, Henry's Law constant, degradation, biodegradation, hydrolysis, photolysis, bioaccumulation, bioconcentration, trophic magnification, removal in wastewater treatment, environmental mobility, environmental fate.*

Search Strategy for Engineering and Exposure

Searches of the peer-reviewed literature, gray literature, and government resources will be conducted to locate any new information on environmental releases, occupational exposure, consumer exposure, general population exposure and environmental exposure. The types of data sought include process description information, monitoring data, modeling data, survey data, and any completed exposure assessments that can be considered representative and relevant. Search terms will include the CASRN, chemical name, synonyms, trade names, and common misspellings, and the following terms (or abbreviations thereof):

> *aerosol, air, breathing zone, biomonitoring, building envelope, chamber, children, commercial, consumer, crawling, cultural, cumulative, dermal, disadvantaged, disease, disposal, dose, drinking water, dust, effluent, elderly, emission, engineering control, environmental justice, ethnicity, excretion, exposure, facility, fence-line population, fetal, fetus, flux, gender, general population, genetic, geriatric, ground water, hand-to-mouth, health status, household, homeless, illegal immigrant, immunocompromised, import, incinerate, income, indigenous, indoor, industrial, infant, influent, ingestion, inhalation, intake, lactate, landfill, lifecycle, manufacture, menopause, metabolism, monitoring, mouthing, near-facility population, nutrition status, occupation, ocular, older adults, on-site treatment, oral, occurrence, pathway, penetration, pica, placenta, plasma, plume, personal care, point source, postnatal, POTW, PPE, pre-existing disease, pregnant,*

prenatal, preparedness, pretreatment program, process, product, protective, proximity, race, recover, recreation, recycling, release, residential, residual, route, rural, sample, school-age, sediment, senior, sensitive, serum, sewage treatment, short term, shower, single parent, sink, site, skin, sludge, socioeconomic status, soil, source, stress, subpopulation, subsistence, subsurface intrusion, Superfund, surface water concentration, susceptible, time-weighted average, toddler, transfer, tribal, urban, urine, use, vapor, ventilation, volume, vulnerable, wastewater treatment, water, weight fraction, wipe, women of childbearing age, worker, workplace, WWTP, young.

Use terms (for example *additive*, *adhesion*, *antifoam*, *automotive*, *coating*, *conditioner*, *cream*, *electronic*, *fluid*, *foaming*, *gel*, *grease*, *lotion*, *lubricant*, *mold*, *oil*, *paste*, *rubber*, *sealant*, *shampoo*, *skin*, *textile*, etc.) may be added depending on the findings of the search for uses and the results of the user survey.

Search Strategy for Human Health Hazard

The search for new information on human health hazard will be conducted using PubMed and will use the CASRN and chemical name(s) synonyms, trade names, and common misspellings and the health effect terms as identified in the "Strategy for Conducting Literature Searches for Cyclic Aliphatic Bromine Cluster (HBCD): Supplemental Document for the TSCA Scope Document" (U.S. EPA 2017b). These terms are found in Appendix D.

Search Strategy for Environmental Hazard

A search of the U.S EPA ECOTOX Knowledgebase will be performed to identify any new information on D4. Searches of the peer-reviewed literature, gray literature, and other government resources will also be conducted. The keywords used for these searches will include *CASRN*, *chemical name(s), (including synonyms, trade names, and common misspellings)*, *toxicity*, *ecotoxicity*, *bioassay*, *effect*, *bioaccumulation*, *mortality*, *growth*, *reproduction*, *fish*, *invertebrate*, *alga*/*algae*, *plant*, *sediment*, *benthic*, and *aquatic*.

Data Search Process, Results, and QA/QC

The data search for each topical area will be conducted by an Exponent scientist with expertise in that area. ProQuest DIALOG and ACS STN searches will be conducted by Exponent Information Resources Department staff as directed by a member of Exponent's D4 project team. The results will be compiled, and any duplicates will be removed. The ability of the searches to receive known publications will serve as a QC check on the process.

Data Screening (Title/Abstract)

The results of the data search will be initially screened based on the title and abstract to determine if the item should be included or excluded from further evaluation. Items will be excluded if they meet one or more of the following criteria:

- Do not contain information on D4
- Only contain information on D4 as part of a mixture
- No full text available (e.g., only a presentation abstract)
- Are already in Exponent's possession.

The exclusion criteria may be adjusted based on initial findings. For example, information in certain topic areas that refers to D5 (decamethylcyclopentasiloxane) or D6 (dodecamethylcyclohexasiloxane) may be relevant.

A list of items considered to be included for further evaluation will be organized by topic area and cross-checked for duplication. This list will be reviewed by Exponent project management, who will resolve any conflicts or issues, and will be provided to SEHSC for acquisition of the items. The original list as well as the lists for further evaluation will be retained in the project documentation.

Data Screening/Full Text

Items that have been acquired, organized by topic area, will be assigned for review by scientists familiar with the topic (e.g., chemists, ecotoxicologists, mammalian toxicologists, etc.). The

screening process for full text will result in inclusion or exclusion of the item based on fulfillment of criteria for each topical area presented below.

Physico-chemical properties

To be included, the item must adequately characterize the test substance, must report data on a relevant physico-chemical property, and must discuss the methodology used.

Conditions of Use

Items are eligible for inclusion if they provide information on the following:

- Manufacturing, processing, distribution, use or disposal data, or relevant information about D4
- Trends in manufacturing (including import) volumes of D4
- Number and location of sites that manufacture, process, distribute, use, recycle, or dispose of D4
- Functional uses for D4
- Which industry sectors use D4
- What concentrations (weight fraction) of D4 are used in industrial, commercial, and consumer applications
- What types of products or articles contain D4
- Methods of distribution, e.g., internet sales
- What volume of D4 is used for each type of use
- Which uses have been discontinued or phased out
- The likelihood that other chemicals will replace D4 and the names of the other chemicals
- The likelihood that D4 will replace other chemicals with similar functional uses
- Uses for recycled materials containing D4 and volume of material recycled
- Approximate number and description of individuals who can be exposed to D4, e.g., industrial workers, commercial workers, high-frequency consumer use, low-frequency consumer use, and children
- The typical setting for uses (e.g., outdoors, indoors, industrial commercial, residential, vehicular).

Data or information not within these characteristics are excluded from further evaluation.

Environmental Fate

EPA describes the use of PECO (Population, Exposure, Comparator, and Outcome) statements during full text review (U.S. EPA 2018). These statements are used to formulate explicit and detailed criteria about the characteristics of data/information that should be present to be eligible for inclusion in the review. This approach, adjusted slightly for each topic area (e.g., PESO for environmental fate, RESO for engineering and occupational exposure), has been adopted for the full text screening of D4 information.

For environmental fate, items that address the criteria in Table 3 are eligible for inclusion and considered for further evaluation.

Table 3. Inclusion criteria for data sources reporting environmental fate data

PESO Element	Evidence
Pathways and **P**rocesses	Environmental fate, transport, partitioning, and degradation behavior across environmental media to inform exposure pathways of the chemical substance of interest Media of interest may include: – Air – Surface water – Ground water – Soil – Sediment – Biosolids – Other media including anthropogenic materials and media in the indoor environment (e.g., dust).
Exposure	Environmental exposure of ecological receptors (i.e., aquatic and terrestrial organisms) to the chemical substance of interest and/or its degradation products and metabolites. Environmental exposure of human receptors, including any potentially exposed or susceptible subpopulations, to the substance of interest and/or its degradation products and metabolites.
Setting or **S**cenario	Any setting or scenario resulting in releases of the chemical substance of interest into the natural or built environment (e.g., buildings including homes or workplaces, or wastewater treatment facilities) that would expose ecological (i.e., aquatic and terrestrial organisms) or human receptors (i.e., consumers, general population, and potentially exposed or susceptible subpopulation).
Outcomes	Fate properties which allow assessments of exposure pathways: o Abiotic and biotic degradation rates, mechanisms, pathways, and products o Bioaccumulation magnitude and metabolism rates o Partitioning within and between environmental media.

Engineering and Occupational Exposure

Items that address the criteria in Table 4 are eligible for inclusion and considered for further evaluation.

Table 4. Inclusion criteria for data sources reporting engineering and occupational exposure data

RESO Element	Evidence
Receptors	**Humans:** Workers, including occupational non-users. **Environment:** Aquatic and possibly terrestrial ecological receptors (release estimates input to Exposure).
Exposure	Worker exposure to and relevant environmental releases of D4 o Any exposure route indicated in the conceptual site models o Any relevant media/pathway as indicated in the conceptual site models.
Setting or **S**cenario	Any occupational setting or scenario resulting in worker exposure and environmental releases (includes all manufacturing, processing, use, and disposal).
Outcomes	Quantitative estimates of worker exposures and of relevant environmental releases from occupational settings. General information and data related and relevant to the occupational estimates.

Exposure Data for General Population, Consumers, and Ecological Receptors

Items that address the criteria in Table 5 are eligible for inclusion and considered for further evaluation.

Table 5. Inclusion criteria for the data sources reporting D4 exposure data on general population, consumers, and ecological receptors

PECO Element	Evidence
Population	**Human:** Different human population groups may be exposed to D4, including potentially exposed or susceptible subpopulations (e.g., children, susceptible life stages, people with preexisting conditions or genetic factors, pregnant women, women of child bearing age, infants), general population exposures through all relevant media, populations with subsistence diets, near facility populations, consumers, and bystanders. Also consider typical and potentially highly exposed groups within these general categories. Human biomonitoring data to be considered.
	Ecological: Aquatic biota (fish, benthic invertebrates, pelagic invertebrates, algae, aquatic plants). Wildlife biomonitoring data to be considered.
Exposure	**Expected Primary Exposure Sources, Pathways, Routes:** - Sources: manufacturing, processing, use, and disposal - Pathways: indoor and outdoor air, sediment; media-specific background and source attribution to be considered. - Routes of Exposure dermal, and Inhalation (indoor and outdoor air) for human receptors; ingestion and contact (sediment/soil) for ecological receptors. **Expected Lesser Exposure Sources, Pathways, Routes** - Sources: manufacturing, processing, use, and disposal of products containing D4 and associated releases to water, or solid wastes. Indoor sources/materials that are less prevalent and/or contain relatively low concentrations of D4. - Pathway: indoor and outdoor air, media-specific background and source attribution to be considered. - Routes of Exposure: inhalation; dermal (contact with surface water, contact with products/materials) oral (incidental) for human receptors
Comparator (Scenario)	**Human:** Consider media-specific background exposure scenarios and use/source specific exposure scenarios as well as which receptors are and are not reasonably exposed across the projected exposure scenarios.
	Ecological: Consider media-specific background exposure scenarios and use/source specific exposure scenarios as well as which receptors are and are not reasonably exposed across the projected exposure scenarios.
Outcomes for Exposure Concentration or Dose	**Human:** Both external potential dose and internal dose based on ADME data, biomonitoring and reverse dosimetry mg/kg/day will be considered (to compare with a wide range of health effects following acute through chronic exposures).
	Ecological: Surface water concentrations and sediment concentrations will be used (to compare with metrics used for ecological toxicity values). Wildlife biomonitoring data such as in fish.

Human Health Hazard

Items that address the criteria in Table 6 are eligible for inclusion and considered for further evaluation. This table also specifies exclusion criteria.

Table 6. Inclusion and exclusion criteria for data sources reporting human health hazards related to D4 exposure.

PECO Element	Evidence Stream	Papers/Features Included	Papers/Features Excluded
Population	*Human*	Any population All life stages All study designs: o Controlled exposure, cohort, case-control, cross-sectional, case-crossover, ADME, biomonitoring, physiologically based pharmacokinetic (PBPK modeling	
	Animal	All standard whole-organism mammalian species, including rat, mouse, hamster, rabbit, guinea pig, monkey, dog All life stages	Wildlife species Non-mammalian species Agricultural species/livestock
	Mechanistic	Human or animal cells (including nonmammalian model systems), tissues, or biochemical reactions (e.g., ligand-binding assays); bioinformatics pathways of disease analysis; or high-throughput screening data.	
Exposure	*Human and Animal*	Exposure to an administered dose or concentration of D4 Exposure is measured as a concentration in an environmental medium (e.g., air, dust, soil, diet) or biological fluid or tissue (e.g., blood, milk, urine, adipose tissue), or administered as a controlled dose Exposure is in vivo Exposure identified as ***or presumed to be*** from oral, dermal, and inhalation routes	Not a chemical specific (study population is not exposed to D4) Exposure is to a mixture only, i.e., simultaneous exposure to other chemicals in addition to D4 Exposure via injection or implant
	Mechanistic	Exposure based on concentrations of D4	
Comparato**r**	*Human*	A comparison population [not exposed, exposed to lower levels, exposed below detection] for all endpoints	No comparison population for endpoints
	Animal and Mechanistic	Negative controls that are vehicle-only treatment and/or no treatment	Negative controls ***other than*** vehicle-only treatment or no treatment
Outcom**e**	*Human and Animal*	Health Endpoints Typical acute, subchronic and chronic endpoints Irritation Sensitization Liver effects Endocrine/thyroid effects Developmental effects Immune effects Neurological effects Reproductive effects Carcinogenicity/mutagenicity Target organs (	No health outcome evaluated (e.g., a study of D4 exposure levels)
	Mechanistic	Mechanistic data that supports the characterization of the identified endpoints of interest	

Ecological Hazard

The criteria for inclusion/exclusion for ecotoxicological data are those used in the ECOTOX Knowledgebase (https://cfpub.epa.gov/ecotox/help.cfm). These are captured in Table 7.

Table 7. Inclusion and exclusion criteria for data sources reporting ecological hazards to D4 exposure

Criteria	Requirement/Inclusions	Limitations/Exclusions
Chemical	Single chemicals relevant to environmental exposure are included. Verifiable Chemical Abstract Services (CAS) number	Mixtures Air pollution (CO_2, ozone)
Species	Ecologically relevant species Priority species are wild (test results for terrestrial domestic and laboratory species are used to fill data gaps when needed) Organism taxonomic information verifiable against standard taxonomic sources	Human, monkey, bacteria, virus, and yeast
Effect/Response	Biological effect on live, whole organisms Adverse effects are priority (beneficial, nutritional effects are lower priority)	Dead organisms
Concentration/Dose	Concurrent environmental chemical concentration/dose reported as concentration, dose or application rate	Inhalation studies route (including intratracheal instillation) Sediment only concentration Lead shot Unverified measurement unit Log values
Exposure Duration	Duration reports are associated concurrent with a biological effect	Unverifiable duration
Publication/Data Format	Primary data source Full text English (some Non-English papers are encoded that have an English abstract)	Reviews Full text foreign language Abstract only format

The output from the full text data screening step will be a list (or table or spreadsheet) of the items considered to be excluded vs. included, organized by topic area. A brief rationale will be provided for items that are excluded. Items that are included will proceed to the data extraction step.

Data Extraction and Evaluation

The steps of data extraction and evaluation have been combined for efficiency. This phase of the process considers the reliability of the data/information. The relevance of the information for use in the risk evaluation is considered in the data integration step.

Various approaches have been proposed to evaluate data quality, as reviewed by Ägerstrand et al. (2011) and Bevan and Strother (2012). Traditionally, the most widely used approach is that of Klimisch et al. (1997), but this approach has been criticized (whether fairly or not) for its reliance on GLP compliance. The approach proposed for this project is derived from that developed by EPA in its recent guidance for systematic review (U.S. EPA 2018).

Data and information from items retained for full text evaluation, according to the inclusion criteria presented previously, are extracted into topic-specific templates. These templates facilitate the data evaluation and data integration processes. In the extraction step, brief descriptions of the relevant information are captured for each information element. In the evaluation step, a score is assigned to reflect the quality of the information. The possible scores for each information element are:

- 1 (high): adequate and appropriate information
- 2 (medium): minor uncertainties or limitations, unlikely to have a significant impact on the results
- 3 (low): data not reported or deficiencies likely to have a significant impact on the results
- 4 (unacceptable): serious flaws or key information missing that renders the data unusable.

Short questions are provided in the templates to indicate the basis for the evaluation, but the evaluator will be referred to further details in EPA's systematic review guidance (U.S. EPA 2018). The goal for the scoring system is to increase objectivity, transparency, and consistency. The rationale for the scores assigned will be briefly documented in the template. Weighting factors for the scores are not proposed at this time. Note that the range of total possible scores is

provided in each template. The lower the total score, the more reliable the information. These scores are useful for comparing data within a particular topic area but not between topic areas.

Members of the Exponent D4 project team will be assigned to perform data extraction and evaluation by discipline, e.g., toxicologists will work on human health hazard information, ecotoxicologists will work on ecological hazard information, etc.

Physico-chemical property data

The template for extracting and evaluating physico-chemical property data is provided in Table 8. This template is to be used primarily for experimental data. Physico-chemical property data that are from a recognized data collection/repository, where data are reviewed by experts in the field, that are broadly available to the public, and that include references to the original sources will be given the highest score (most reliable) of 6. If the source is of a lesser quality, the score will be adjusted accordingly and the rationale provided.

Table 8. Template for extracting and evaluating physico-chemical property data

Short citation (Author, year, or ID)			
Full citation (or link)			
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity		Was the test substance identified definitively?	
Composition (purity, origin); single substance (not mixture)		Was the source and purity identified?	
Test Design			
Test system		Were appropriate methods used?	
Test conditions		Were the test conditions appropriate?	
Methods and Observations			
Analytical or other methods described		Was the test substance analytically verified in the test system using appropriate methods?	
Results			
Findings described		Were the findings consistent with the methodology?	
		Range of possible scores	6–24

The template for extracting environmental fate data is provided in Table 9.

Table 9. Template for extracting and evaluating environmental fate data

Short citation (Author, year, or ID)			
Full citation (or link)			
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity		Was the test substance identified definitively?	
Composition (purity, origin); single substance (not mixture)		Was the source and purity identified?	
Preparation		Was the test substance preparation described and appropriate for the test system?	
Test Design			
Test system (suitability)		Was the test method appropriate for the test substance?	
Test conditions (monitored and appropriate)		Were test conditions appropriate?	
Consistency (across groups)		Were test conditions consistent across groups?	
Test organisms (if applicable)		Was the inoculum or test organism appropriate?	
Controls		Were the appropriate controls used?	
Duration		Was the duration of the study appropriate?	
Methods and Observations			
Observations (half-lives, coefficients, etc.)		Were the appropriate outcomes reported?	
Control performance		Was control performance acceptable?	
Sampling adequacy (frequency, duration)		Was the timing and frequency of sampling adequate?	
Analytical method and measurements of test substance to verify presence in test system		Were appropriate methods of analysis used?	
Results			
Confounding variables		What sources of variability were noted and did they affect the outcome assessment?	
Outcomes unrelated to exposure		Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	
Data		Were the data appropriately reported to document the outcome(s)?	
Statistical method and kinetic calculations		Were statistics and/or kinetic calculations described and consistent?	
Plausibility of results		Were the study results reasonable?	
		Range of possible scores	18–72

Engineering and Occupational Exposure

Information related to engineering and environmental releases, and occupational exposure, are generally not found in controlled studies. The types of data sources most likely to be useful include monitoring data, environmental release data, published models for exposures or

releases, completed exposure or risk assessments, and other reports. Data extraction and evaluation templates for general life-cycle and facility data, occupational exposure data, and environmental release data are provided in Tables 10, 11, and 12, respectively.

Table 10. Template for extracting and evaluating general life-cycle and facility data

Short citation (Author, year, or ID)		
Full citation (or link)		
General Life-Cycle and Facility Data (note: these apply to both occupational exposure and environmental releases)		
Life-cycle stage		
Life-cycle description (subcategory of use)		
Process description		
Total annual U.S. volume		
Number of sites		
Batch size		
Operating days per year and batches per day		
Site daily throughput		
Possible physical form		
Chemical concentration		
Data Quality Evaluation		
	Data and Rationale for Score	Score
Reliability		
Methodology		
Representativeness		
Geographic Scope		
Applicability		
Temporal representativeness		
Sample size		
Accessibility/Clarity		
Metadata completeness		
Variability and Uncertainty		
Metadata completeness		
	Range of possible scores	7–28

Table 11. Template for extracting and evaluating occupational exposure data

Short citation (Author, year, or ID)		
Full citation (or link)		
Occupational Exposure Data		
Life-cycle stage		
Physical form		
Route of exposure		
Exposure concentration (unit)		
Number of samples		
Number of sites		
Type of measurement (e.g., TWA, STEL) or method (e.g., modeling)		
Worker activity (or source of exposure if stationary sampling) or job description		
Number of workers		
Type of sampling (e.g., personal, pump/passive, stationary)		
Sampling location/key environmental factors (e.g., temperature, humidity)		
Exposure duration		
Exposure frequency		
Engineering control and % exposure reduction		
Personal protective equipment (PPE)		
Analytic method		
Data Quality Evaluation		
	Data and Rationale for Score	Score
Reliability		
Methodology		
Representativeness		
Geographic Scope		
Applicability		
Temporal representativeness		
Sample size		
Accessibility/Clarity		
Metadata completeness		
Variability and Uncertainty		
Metadata completeness		
	Range of possible scores	7–28

Table 12. Template for extracting and evaluating environmental release data

Short citation (Author, year, or ID)		
Full citation (or link)		
Environmental Release Data		
Life-cycle stage		
Release source (at the process- or unit-level with the type of waste)		
Disposal/treatment method		
Environmental media		
Release or emission factor		
Release estimation method		
Daily and annual release quantity (kg/day and kg/year)		
Release days per year		
Number of sites		
Waste treatment method		
Pollution preventions/control and % efficiency		
Data Quality Evaluation		
	Data and Rationale for Score	Score
Reliability		
Methodology		
Representativeness		
Geographic scope		
Applicability		
Temporal representativeness		
Sample size		
Accessibility/Clarity		
Metadata completeness		
Variability and Uncertainty		
Metadata completeness		
	Range of possible scores	7–28

Consumer, General Population, and Environmental Exposure

Sources of information for consumer, general population, and environmental exposure include monitoring data, modeling data, survey-based data, epidemiological data, experimental data, completed exposure assessments and risk characterizations, and other sources. Templates are provided for data extraction and evaluation for the two most likely sources of data for the D4 risk evaluation: monitoring data (Table 13) and completed exposure assessments and risk characterizations (Table 14). If other data sources are located, templates will be developed as needed.

Table 13. Template for extracting and evaluating monitoring data

Short citation (Author, year, or ID)			
Full citation (or link)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Reliability			
Sampling methodology		Did the sampling methods follow sound and widely accepted or appropriate Standard Operating Procedures?	
Analytical methodology		Did the analytical methods follow sound and widely accepted or appropriate methodology?	
Selection of biomarker of exposure		Is the biomarker in the specified matrix highly related to exposure?	
Representativeness			
Geographic area		Is the geographic area reported and well-described?	
Currency		Is the timing of sampling consistent with current or recent exposures?	
Spatial and temporal variability		Does the sampling approach accurately capture variability?	
Exposure scenario		Does the data closely represent a relevant exposure scenario (e.g., media of interest)?	
Accessibility/Clarity			
Reporting of results		Are summary statistics provided or the data available to allow their calculation?	
Quality assurance		Were QA/QC measures applied and are they described?	
Variability and Uncertainty			
Variability and uncertainty		Does the study characterize variability and identify key uncertainties?	
		Range of possible scores	10–40

Table 14. Template for extracting and evaluating completed exposure assessments and risk characterizations

Short citation (Author, year, or ID)			
Full citation (or link)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Reliability			
Methodology		Does the assessment use approaches that are generally accepted by the scientific community? Are assumptions described? Are calculations correct?	
Representativeness			
Exposure scenario		Does the data closely represent exposure scenarios of interest?	
Accessibility/Clarity			
Documentation of references		Are references provided and from quality sources?	
Variability and Uncertainty			
Variability and uncertainty		Does the study characterize variability and identify key uncertainties?	
		Range of possible scores	4–16

Human health hazard data

The templates for extracting human health hazard data are provided in Table 15 (for animal toxicity studies) and Table 16 (for in vitro studies).

Table 15. Template for extracting and evaluating human health hazard data: animal toxicity studies

Short citation (Author, year, or ID)			
Full citation (or link)			
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity		Was the test substance identified definitively?	
Composition (purity, origin); single substance (not mixture)		Was the source and purity identified?	
Preparation		Was test substance preparation described and appropriate for the test system?	
Test Design			
Test conditions		Were the husbandry conditions appropriate?	
Test organisms (species, age, health, handling)		Was the test species and strain appropriate?	
Controls (negative, vehicle, positive)		Were the appropriate controls used?	
Number of animals per group		Was the number of animals per group appropriate?	
Randomized design		Were animals randomly allocated to groups?	
Exposure Characterization			
Exposure consistency		Were exposures consistent across groups?	
Exposure route and method		Was the exposure route and method appropriate?	
Exposure period (length, dosing frequency)		Was the exposure frequency and duration appropriate?	
Treatment groups (concentrations/doses/rates; spacing)		Was the number of groups appropriate?	
Measurement of test substance concentrations		Were exposures analytically verified?	
Methods and Observations			
Control organism performance		Were the biological responses of the negative control group adequate?	
Outcome assessment methodology		Was the outcome assessment methodology sensitive for the outcome(s) of interest?	
Consistency of outcome assessment		Was the outcome assessment done consistently across groups?	
Sampling adequacy		Was sampling adequate for the outcomes of interest?	
Blinding of assessors for subjective outcomes (if applicable)		Were assessors of subjective outcomes blinded to treatment groups?	
Confounding variables in design/procedures		Were there confounding differences among groups that could influence the outcome?	
Results			
Outcomes unrelated to exposure		Were there differences in study groups that were unrelated to exposure that could influence the outcome?	
Data		Were the data appropriately reported to document the outcome(s)?	
Statistical methods		Were statistical methods appropriate?	
		Range of possible scores	21–84

Table 16. Template for extracting human health hazard data: In vitro studies

Short citation (Author, year, or ID)			
Full citation (or link)			
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity		Was the test substance identified definitively?	
Composition (purity, origin); single substance (not mixture)		Was the source and purity identified?	
Preparation		Was test substance preparation described and appropriate for the test system?	
Test Design			
Test model		Were test models reported and appropriate?	
Assay procedures		Were assay procedures appropriate?	
Controls (negative, vehicle, positive)		Were the appropriate controls included?	
Number of groups and/or replicates described		Was the number of groups and replicates appropriate?	
Exposure Characterization			
Exposure consistency		Were exposures consistent across groups?	
Metabolic activation (if applicable)		Was metabolic activation appropriate?	
Exposure duration		Was the exposure duration appropriate?	
Treatment groups (concentrations/doses)		Was the number of exposure groups and dose spacing appropriate?	
Reporting of concentrations		Were exposure doses/concentrations reported clearly?	
Methods and Observations			
Control performance		Was control performance adequate?	
Outcome assessment methodology		Was the outcome assessment methodology sensitive for the outcome(s) of interest?	
Consistency of outcome assessment		Was the outcome assessment done consistently across groups?	
Sampling adequacy		Was sampling adequate for the outcomes of interest?	
Blinding of assessors for subjective outcomes (if applicable)		Were assessors of subjective outcomes blinded to treatment groups?	
Confounding variables in design/procedures		Were there confounding differences among groups that could influence the outcome?	
Results			
Outcomes unrelated to exposure		Were there differences in study groups that were unrelated to exposure that could influence the outcome?	
Data		Were the data appropriately reported to document the outcomes?	
Data analysis		Were statistical methods and calculations appropriate?	
Data interpretation		Were the evaluation criteria appropriate?	
Cytotoxicity		Were cytotoxicity endpoints described?	
		Range of total scores	23–92

Ecological effects data

The template for extracting and evaluating ecological effects data is provided in Table 17.

Table 17. Template for extracting and evaluating ecotoxicology data

Short citation (Author, year, or ID)			
Full citation (or link)			
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity		Was the test substance identified definitively?	
Composition (purity, origin); single substance (not mixture)		Was the source and purity identified?	
Preparation		Was test substance preparation described and appropriate for the test system?	
Test Design			
Test system (field, lab, static, flow-through, open/closed, etc.)		Was the test system appropriate for the test substance and desired outcome(s)?	
Test conditions (test vessels, pH, temperature, media, etc.)		Were the test conditions appropriate?	
Test organisms (species, age, health, handling)		Was the test species, age, etc. appropriate?	
Test organism acclimation		Were test organisms acclimated appropriately?	
Controls (negative, vehicle, positive)		Were the appropriate controls used?	
Number of organisms and replicates per group		Was the number of organisms and replicates per group appropriate?	
Number of exposure groups and spacing		Were the number of exposure groups and spacing between them appropriate?	
Randomized design		Were organisms randomly allocated to groups?	
Exposure Characterization			
Testing at or below solubility		Were exposure concentrations at or below the water solubility limit? Was the solvent concentration appropriate?	
Exposure consistency		Were exposures consistent across groups?	
Exposure route and method (aqueous, via soil, etc.)		Was the exposure route and method appropriate?	
Exposure period (length, dosing frequency)		Was the exposure frequency and duration appropriate?	
Treatment groups (concentrations/doses/rates)		Was the number of groups and spacing of doses appropriate?	
Measurement of test substance concentration		Were test substance concentrations measured if poorly water soluble?	
Methods and Observations			
Control organism performance		Were the biological responses of the negative control group adequate?	
Outcome assessment methodology		Was the outcome assessment methodology sensitive for the outcome(s) of interest?	
Consistency of outcome assessment		Was the outcome assessment done consistently across treatment groups?	

Sampling adequacy		Was sampling adequate for the outcome(s) of interest?	
Confounding variables in design/procedures		Were there confounding differences among groups that could influence the outcome?	
Results			
Data		Were the data appropriately reported to document the outcome?	
Outcome unrelated to exposure		Were there differences in study groups that were unrelated to exposure that could influence the outcome?	
Statistical methods		Were statistical methods appropriate?	
Estimate of variability		Were unexpected outcomes explained and variability discussed?	
		Range of scores	26–104

A template has not been developed for epidemiology data at this time. If such data is located, a template will be created before evaluating the data.

QA/QC

More senior members of the Exponent D4 project team with relevant experience will review the data extraction and evaluation performed by other team members. The evaluation of each study/data source will be reviewed by someone other than the initial evaluator. If the reviewer reaches a different conclusion than the original evaluator, a discussion will be had to resolve the difference.

Data Integration

In the data evaluation stage, described previously, the reliability of individual studies/information is assessed. In the data integration stage, the information is analyzed and synthesized. The relevance of each study/information for use in the D4 risk evaluation is considered in this step. The difference between reliability and relevance was defined by Ägerstrand et al (2011):

> *Reliability evaluation has to do with how well-characterized the test model is and if the reporting is sufficient to ensure the reproducibility of the test. The relevance evaluation has to do with the appropriateness of the test when it comes to a particular risk, e.g. whether the experimental model is representative [of] the environment that is aimed to be protected.*

It is possible for these attributes to be independent of each other. A study can have a very high degree of reliability (e.g., appropriate methods, good documentation, correct statistical approach) but be irrelevant for the risk assessment question at hand. Conversely, the study can be quite relevant but be so poorly reported as to be unreliable. Therefore, reliability and relevance should be evaluated separately.

The data integration stage considers reliability, relevance, consistency, coherence, and biological plausibility to develop a weight-of-evidence argument synthesizing multiple evidence streams to support the hazard assessment, exposure assessment, and risk characterization. For each evidence stream, the information will be summarized, and the strengths and limitations will be discussed. For example, in vitro toxicity data and animal toxicity data are two different evidence streams that are both used for human health hazard assessment. Information is then integrated across evidence streams, accounting for the strengths, limitations, and relevance of each. For example, the use of a Quantitative Structure-Activity Relationship (QSAR) model to estimate aquatic toxicity is an evidence stream that is considered to contribute less to the overall weight-of-evidence than experimental whole-organism toxicity data. The data integration will also present the underlying assumptions, address the uncertainties that require consideration, and highlight the major points of interpretation. Professional judgment will be applied transparently, and its application will be clearly documented.

QA/QC

The data integration findings will be used in the risk evaluation report, which will be assigned a unique QA ID number and will undergo review following Exponent's quality management system procedures.

This includes technical review by team members other than those who prepared the findings, editorial review, and senior-level review by a principal of the firm.

References

Ägerstrand, M., A. Küster, J. Bachmann, M. Breitholtz, I. Ebert, B. Rechenberg, and C. Rudén. 2011. Reporting and evaluation criteria as a means towards a transparent use of ecotoxicity data for environmental risk assessment of pharmaceuticals. Environ. Pollut. 159:2487–2492.

Bevan, C., and D. Strother. 2012. Best practices for evaluating method validity, data quality and study reliability of toxicity studies for chemical hazard and risk assessments. Developed for ACC's Center for Advancing Risk Assessment Science and Policy, December 2012. Available at http://arasp.americanchemistry.com/.

Brooke, D.N., M.J. Crookes, D. Gray, and S. Robertson. 2009. Environmental Risk Assessment Report: Octamethylcyclotetrasiloxane. ISBN: 978-1-84911-031-0. UK Environment Agency. April.

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Klimisch, H.J., M. Andreae, and U. Tillmann. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1–5.

U.S. EPA. 2017a. Guidance to Assist Interested Persons in Developing and Submitting Draft Risk Evaluations Under the Toxic Substances Control Act. EPA 740-R17-001. U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention. June 2017.

U.S. EPA. 2017b. Strategy for Conducting Literature Searches for Cyclic Aliphatic Bromine Cluster (HBCD): Supplement Document to the TSCA Scope Document. U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention. June 2017.

U.S. EPA. 2018. Application of Systematic Review in TSCA Risk Evaluations. EPA Document # 740-P1-8001. U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention. May 2018.

Appendix A

Table A2. List of U.S. state sources for D4 literature searches

State	Type	Title	URL
Alabama	Environment	Alabama Department of Environmental Management	www.adem.state.al.us
Alabama	Environmental Health/Public Health	Alabama Department of Public Health	www.adph.org/environmental
Alabama	Occupational Health	Alabama Occupational Safety and Health	www.labor.alabama.gov
Alaska	Environment	Alaska Department of Environmental Conservation - State of Alaska	www.dec.alaska.gov
Alaska	Occupational Health	Alaska Occupational Safety and Health Section	www.labor.state.ak.us/lss/oshhome.htm
Arizona	Environmental Health/Health	ADEQ Arizona Department of Environmental Quality	www.azdeq.gov
Arizona	Environmental Health/Health	Arizona Department of Health Services	www.azdhs.gov
Arizona	Occupational Health	ADOSH Main Page | Industrial Commission of Arizona	www.azica.gov/our-organization/adosh
Arkansas	Environment	Arkansas Department of Environmental Quality (ADEQ)	www.adeq.state.ar.us
Arkansas	Environmental Health/Health	ADH: Environmental Health - Arkansas Department of Health	www.healthy.arkansas.gov
Arkansas	Occupational Health	Occupational Health and Safety Compliance Program	www.labor.arkansas.gov/occupational-safety-and-health-compliance-program- aosh
California	Environment	California Department of Conservation	www.conservation.ca.gov
California	Environment	California Department of Toxic Substances Control	www.dtsc.ca.gov
California	Environment	California Environmental Protection Agency: CalEPA	www.calepa.ca.gov
California	Environmental Health/Health	Biomonitoring California	www.biomonitoring.ca.gov
California	Environmental Health/Health	Office of Environmental Health Hazard Assessment	www.oehha.ca.gov
California	Occupational Health	Cal/OSHA - Division of Occupational Safety and Health	www.dir.ca.gov/dosh
California	Occupational Health	California Department of Public Health	www.cdph.ca.gov
California	Occupational Health	California permissible exposure limits for chemical contaminants	https://www.dir.ca.gov/title8/5155table_ac1.html
California	Environmental Health/Health	California Department of Toxic Substances Control Toxics in Products	http://www.dtsc.ca.gov/PollutionPrevention/ToxicsInProducts/index.cfm http://www.dtsc.ca.gov/SCP/CandidateChemicalsList.cfm http://www.dtsc.ca.gov/SCP/WhatIsAPriorityProduct.cfm
California	Environmental Health/Health	California hazardous substance list	https://www.dir.ca.gov/title8/339.html
California	Environmental Health/Health	California Office of Environmental Health Hazard Assessment Proposition 65	http://oehha.ca.gov/proposition-65/chemicals http://oehha.ca.gov/proposition-65/proposition-65-list
California	Environmental Health/Health	California Safe Cosmetics Program – list of chemical agents known or suspected to cause cancer or developmental or other reproductive harm.	https://safecosmetics.cdph.ca.gov/search/Default.aspx
Colorado	Environmental Health/Health	Colorado Department of Public Health and Environment	www.cdphe.state.co.us
Connecticut	Environment	Connecticut Department of Energy & Environmental Protection	www.ct.gov/deep/site/default
Connecticut	Environmental Health/Health	Department of Public Health: Environmental Health	www.ct.gov/dph/
Connecticut	Occupational Health	DPH: Occupational Health Unit - CT.gov	www.ct.gov/dph/occupationalhealth
Connecticut	Occupational Health	Occupational Safety & Health (CONN-OSHA) - State of Connecticut	www.ctdol.state.ct.us/osha/osha.htm
Delaware	Environment	Delaware Department of Natural Resources and Environmental Control	www.dnrec.state.de.us

Table A2. List of U.S. state sources for D4 literature searches

State	Type	Title	URL
Delaware	Environment	State of Delaware - Topics - Environment	www.delaware.gov/topics/environment
Delaware	Environmental Health/Health	Division of Public Health - Delaware Health and Social Services	www.dhss.delaware.gov/dhss/dph/
Delaware	Occupational Health	Delaware Office of Occupational Health	www.dhss.delaware.gov/dph/hsp/oh.html
Florida	Environment	Florida Department of Environmental Protection (DEP)	www.dep.state.fl.us
Florida	Environmental Health/Health	Florida Health	www.floridahealth.gov/environmental-health/
Georgia	Environment	Georgia Dept. of Natural Resources | Environmental Protection Division	www.epd.georgia.gov
Georgia	Environmental Health/Health	Georgia Department of Public Health	www.dph.georgia.gov/environmental-health
Georgia	Occupational Health	Georgia Occupational Health and Safety Surveillance Program	www.dph.georgia.gov/georgia-occupational-health-and-safety-surveillance-program
Hawaii	Environmental	Hawaii Office of Enviornmental Quality Control	http://health.hawaii.gov/oeqc/
Hawaii	Environmental Health/Health	Hawaii State Department of Health	http://health.hawaii.gov/
Hawaii	Occupational Health	Hawaii Occupational Safety and Health - Department of Labor and Industrial Relations	www.labor.hawaii.gov
Idaho	Environment	Idaho Department of Environmental Quality	www.deq.idaho.gov
Idaho	Environmental Health/Health	Idaho Department of Health and Welfare	www.healthandwelfare.idaho.gov
Illinois	Environment	Illinois Environmental Protection Agency	www.epa.illinois.gov
Illinois	Environmental Health/Health	Illinois Department of Public Health	www.www.idph.state.il.us
Illinois	Occupational Health	Illinois OSHA	www.osha.illinois.gov
Indiana	Environment	Indiana Department of Environmental Management	www.in.gov/idem/
Indiana	Environmental Health/Health	Indiana Environmental Health	www.in.gov/isdh
Indiana	Occupational Health	Indiana Department of Labor OSHA	www.in.gov/dol/iosha.htm
Iowa	Environment	Environmental Protection - Iowa Department of Natural Resources	www.iowadnr.gov
Iowa	Environmental Health/Health	Iowa Department of Public Health-Environmental Health	https://idph.iowa.gov/Environmental-Health-
Iowa	Occupational Health	Iowa OSHA	www.iowaosha.gov
Kansas	Environment	Kansas Department of Health & Environment: Division of Environment	www.kdheks.gov/environment/
Kansas	Environmental Health/Health	Kansas Department of Health & Environment: Division of Public Health	www.kdheks.gov
Kansas	Occupational Health	Kansas Department of Labor: workplace safety	www.dol.ks.gov/Safety
Kentucky	Environment	Department for Environmental Protection	http://dep.ky.gov/Pages/default.aspx
Kentucky	Environment	Kentucky Energy and Environment Cabinet	http://eec.ky.gov/Pages/default.aspx
Kentucky	Environment	Kentucky Environmental Quality Commission	http://eqc.ky.gov/Pages/default.aspx
Kentucky	Environmental Health/Health	Kentucky Cabinet for Health and Family Services	https://chfs.ky.gov/Pages/index.aspx
Kentucky	Occupational Health	Kentucky Labor Cabinet	https://kentucky.gov/government/Pages/AgencyProfile.aspx?AgencyTitle=Labor+Cabinet
Louisiana	Environment	Louisiana Department of Environmental Quality	www.deq.louisiana.gov
Louisiana	Environmental Health/Health	Louisiana Department of Health	www.dhh.louisiana.gov
Maine	Environment	Maine Department of Environmental Protection (DEP)	www.maine.gov/dep/
Maine	Environmental Health/Health	Division of Environmental Health - Maine Department of Health & Human Services	www.maine.gov/dhhs/mecdc/environmental-health/el/

Table A2. List of U.S. state sources for D4 literature searches

State	Type	Title	URL
Maine	Environmental Health/Health	Maine DHHS - Environmental Health	www.maine.gov/dhhs/environmental_health.shtml
Maine	Occupational Health	Maine Department of Labor: Workplace Safety and Health	www.maine.gov/labor/workplace_safety/
Maine	Environmental Health/Health	Maine DEP's chemicals of high concern	http://www.maine.gov/dep/safechem/highconcern/
Maryland	Environment	Maryland Department of the Environment	www.mde.state.md.us
Maryland	Environmental Health/Health	Maryland Department of Health	www.dhmh.maryland.gov
Maryland	Occupational Health	Maryland Department of Labor, Licensing & Regulation	www.dllr.state.md.us
Massachusetts	Environment	Massachusetts Department of Environmental Protection	www.mass.gov/eea/agencies/massdep/
Massachusetts	Environmental Health/Health	Massachusetts Bureau of Environmental Health	www.mass.gov/eohhs/gov/departments/dph/programs/environmental-health/
Massachusetts	Occupational Health	Massachusetts Occupational Health Surveillance Program	www.mass.gov/dph/ohsp
Massachusetts	Environmental Health/Health	Massachusetts Complete list of TURA chemicals	https://www.mass.gov/guides/massdep-toxics-use-reduction-program
Massachusetts	Environmental Health/Health	Lowell Center for Sustainable Production Chemical, Policy and Science Initiative	http://www.chemicalspolicy.org/chemicalspolicy.us.state.database.php
Michigan	Environment	Michigan Department of Environmental Quality	www.michigan.gov/deq/
Michigan	Environmental Health/Health	Michigan Department of Health & Human Services	www.michigan.gov/mdhhs/
Michigan	Occupational Health	MI Occupational Safety & Health Administration - State of Michigan	www.michigan.gov/lara/
Michigan	Environmental Health/Health	Michigan Environmental Health Topics	http://www.michigan.gov/mdhhs/0,5885,7-339-71548_54783_54784_74881-13050--,00.html
Minnesota	Environment	Minnesota Environmental Quality Board	www.eqb.state.mn.us
Minnesota	Environment	Minnesota Pollution Control Agency	www.pca.state.mn.us
Minnesota	Environmental Health/Health	Minnesota Dept. of Health	www.health.state.mn.us
Minnesota	Environmental Health/Health	Environmental Safety - Minnesota.gov	www.mn.gov/portal/health-and-safety/environmental-safety/
Minnesota	Occupational Health	Minnesota Center for Occupational Health and Safety	www.health.state.mn.us/occhealth/
Minnesota	Environmental Health/Health	Minnesota Department of Health Toxic Free Kids Act Chemicals of High Concern	http://www.health.state.mn.us/divs/eh/hazardous/topics/toxfreekids/highconcern.html
Mississippi	Environment	Mississippi Department of Environmental Quality	www.deq.state.ms.us
Mississippi	Occupational Health	Occupational Health - Mississippi State Department of Health	www.msdh.ms.gov
Missouri	Environment	Missouri Department of Natural Resources Division of Environmental Quality	www.dnr.mo.gov/env
Missouri	Environmental Health/Health	Missouri Department of Health & Senior Services	www.health.mo.gov
Missouri	Environmental Health/Health	Kansas Environmental Public Health	www.kcmo.gov/health/environmental-health-services/e
Missouri	Environmental Health/Health	Missouri Environmental Public Health Tracking	https://ephtn.dhss.mo.gov/EPHTN_Data_Portal/data.php
Missouri	Occupational Health	Missouri Department of Labor & Industrial Relations Workplace Safety	www.labor.mo.gov/DLS/workplaceSafety
Montana	Environment	Montana Department of Environmental Quality	www.deq.mt.gov
Montana	Environmental Health/Health	Montana Department of Health | Environmental Health	https://dphhs.mt.gov/publichealth/Environmental-

Table A2. List of U.S. state sources for D4 literature searches

State	Type	Title	URL
Montana	Occupational Health	Montana Department of Labor & Industry Occupational Safety and Health	www.erd.dli.mt.gov/safety-health/occupational-
Nebraska	Environment	Nebraska Department of Environmental Quality	www.deq.state.ne.us
Nebraska	Environmental Health/Health	Nebraska Department of Health & Human Services | Environmental Health	www.dhhs.ne.gov
Nebraska	Occupational Health	Nebraska Department of Labor Office of Safety	www.dol.nebraska.gov/Safety/
Nevada	Environment	Nevada Division of Environmental Protection	www.ndep.nv.gov
Nevada	Environmental Health/Health	Nevada Division of Public and Behavioral Health - State of Nevada, Environmental Health	www.dpbh.nv.gov
Nevada	Occupational Health	Department of Industrial Relations, OSHA	http://dir.nv.gov/OSHA/Home/
New Hampshire	Environment	New Hampshire Department of Environmental Services	www.des.nh.gov
New Hampshire	Environment	Environmental Protection Bureau | NH Department of Justice	www.doj.nh.gov/environmental-
New Hampshire	Environmental Health/Health	New Hampshire Environmental Public Health Tracking Program	www.nh.gov/epht
New Hampshire	Occupational Health	Univ. of NH |Occupational Health Surveillance Program	www.iod.unh.edu/projects/occupational-health-
New Hampshire	Environmental Health/Health	New Hampshire Regulated Toxic Air Pollutants	http://des.nh.gov/organization/commissioner/legal/rules/documents/env-a1400.pdf
New Jersey	Environment	New Jersey Department of Environmental Protection	www.nj.gov/dep
New Jersey	Occupational Health / Environmental Health	NJ Department of Health	www.nj.gov/health/ceohs/
New Jersey	Environmental Health/Health	New Jersey Right to Know Hazardous Substances	http://web.doh.state.nj.us/rtkhsfs/rtkhsl.aspx
New Mexico	Environment	New Mexico Environment Department	www.env.nm.gov
New York	Environment	New York State Department of Environmental Conservation	www.dec.ny.gov
New York	Occupational Health	New York State Occupational Health	https://www.health.ny.gov/environmental/workplace/
North Carolina	Environment	Norht Carolina Department of Environmental Quality	www.deq.nc.gov
North Carolina	Environmental Health/Health	North Carolina Environmental Health	www.nc.gov/agency/environmental-health
North Carolina	Occupational Health	North Carolina Department of Labor, Occupational Health Division	www.nclabor.com/osha/
North Dakota	Environment	Environmental Health Section - North Dakota Department of Health	https://deq.nd.gov/
Ohio	Environment	Ohio EPA Home	www.epa.state.oh.us
Ohio	Environmental Health/Health	Ohio Department of Health | Environmental Health	www.odh.ohio.gov/environmentalhealth
Ohio	Occupational Health	Ohio Bureau of Workers Compensation, Division of Safety & Hygiene services	www.bwc.ohio.gov/employer/programs/safety/
Oklahoma	Environment	Welcome to the Oklahoma Department of Environmental Quality	www.deq.state.ok.us
Oklahoma	Occupational Health	Oklahoma Department of Labor - Safety and Health	https://www.ok.gov/odol/Services/Workplace_Safety_and_Health/
Oregon	Environment	Oregon Department of Environmental Quality	www.oregon.gov/DEQ/
Oregon	Environmental Health/Health	Oregon Public Health Division | Environmental Public Health	www.public.health.oregon.gov/HealthyEnvironments
Oregon	Occupational Health	Oregon Occupational Safety and Health	www.osha.oregon.gov

Table A2. List of U.S. state sources for D4 literature searches

State	Type	Title	URL
Oregon	Environmental Health/Health	Oregon Chemicals of Concern for Children's Health	https://www.oregon.gov/oha/PH/HEALTHYENVIRONMENTS/HEALTHYNEIGHBORHOODS/TOXICSUBSTANCES/Documents/chemicals-of-concern-for-childrens-health.pdf
Oregon	Environmental Health/Health	Oregon Toxic Reductionand Safer Alternatives	https://www.oregon.gov/deq/Hazards-and-Cleanup/ToxicReduction/Pages/default.aspx
Pennsylvania	Environment	Pennsylvania Department of Environmental Protection	www.dep.pa.gov
Pennsylvania	Environmental Health/Health	Pennsylvania Department of Health	https://www.health.pa.gov/Pages/default.aspx#.WLdHiW_ytJ8
Pennsylvania	Occupational Health	Pennsylvania Departmetn of Labor & Industry	www.dli.pa.gov/Individuals/Labor-Management-Relations/bois/Pages/default.aspx
Pennsylvania	Environmental Health/Health	Pennsylvania Department of Labor and Industry Hazardous Substance List	http://www.pacode.com/secure/data/034/chapter323/chap323toc.html
Rhode Island	Environment	Rhode Island Department of Environmental Management	www.dem.ri.gov
Rhode Island	Environmental Health/Health	Rhode Island Department of Health | Environmental Health	www.health.ri.gov/programs/detail.php?pgm_id=1052
Rhode Island	Occupational Health	RI Department of Labor & Training | Workforce Regulation and Safety	www.dlt.ri.gov/occusafe/
Rhode Island	Environmental Health/Health	Rhode Island Air Resources – Air Toxics Regulation	http://www.dem.ri.gov/pubs/regs/regs/air/air22_08.pdf
South Carolina	Environment	South Carolina Health & Saftety | Environment	www.sc.gov/HealthAndSafety/Pages/Enviro
South Carolina	Environmental Health/Health	South Carolina Department of Health & Environmental Control	www.scdhec.gov
South Carolina	Occupational Health	South Carolina Occupational Safety and Health Administration	www.scosha.llronline.com/
South Dakota	Environment	South Dakota Department of Environment & Natural Resources	www.denr.sd.gov
South Dakota	Environmental Health/Health	South Dakota Environmental Health Laboratory	www.doh.sd.gov/lab/environmental/
Tennessee	Environment	Tenneesee Department of Environment & Conservation	www.tennessee.gov/environment/
Tennessee	Environment	Division of Water Resources - TN.Gov	www.tn.gov/environment/section/wr-water-
Tennessee	Environmental Health/Health	Tennessee Department of Health - TN.Gov	www.tn.gov/health/section/eh
Tennessee	Occupational Health	Tennessee Occupational Safety and Health Administration - TN.Gov	www.tn.gov/workforce/section/tosha
Texas	Environment	Texas Commission on Environmental Quality	www.tceq.texas.gov
Texas	Environmental Health/Health	Texas Department of State Health Services, Texas Environmental Health Institute	www.dshs.texas.gov
Texas	Occupational Health	Texas Workforce Commission |OSHA	www.twc.state.tx.us
Texas	Occupational Health	OSHCON: Occupational Safety and Health Consultation Program	https://www.tdi.texas.gov/oshcon/
Utah	Environment	Utah Department of Environmental Quality	www.deq.utah.gov
Utah	Environment	Utah DEQ: Division of Air Quality	www.airquality.utah.gov
Utah	Environmental Health/Health	Utah Environmental Public Health Tracking	www.epht.health.utah.gov
Utah	Occupational Health	Utah Occupational Safety and Health	www.laborcommission.utah.gov/divisions/UOSH/
Vermont	Environment	Vermont Agency of Natural Resources	www.anr.vermont.gov

Table A2. List of U.S. state sources for D4 literature searches

State	Type	Title	URL
Vermont	Environment	Vermont Department of Environmental Conservation	www.dec.vermont.gov
Vermont	Environmental Health/Health	Vermont Department of Health	www.healthvermont.gov
Vermont	Occupational Health	VOSHA | Vermont Department of Labor	www.labor.vermont.gov
Vermont	Environmental Health/Health	Vermont Chemical Disclosure Program for Children's Products	http://www.healthvermont.gov/enviro/chemical/cdp.aspx
Virginia	Environment	The Virginia Department of Environmental Quality: Virginia DEQ	www.deq.virginia.gov
Virginia	Environmental Health/Health	Virginia Department of Health	www.vdh.virginia.gov
Virginia	Occupational Health	Office of Occupational Safety and Health Home	https://www.virginia.gov/services/virginia-occupational-safety-and-health/
Washington	Environment	Access Washington | Environment	www.access.wa.gov/topics/environment
Washington	Environment	Washington State Department of Ecology	www.ecy.wa.gov
Washington	Environmental Health/Health	Washington State Department of Health | Environmental Public Health	www.doh.wa.gov
Washington	Occupational Health	Washington State Department of Labor and Industries | Centers of Occupational Health and Education	www.cohe.lni.wa.gov
Washington	Environmental Health/Health	Washington Chemicals of High Concern to Children	http://www.ecy.wa.gov/programs/hwtr/rtt/cspa/chcc.html
Washington	Environmental Health/Health	Washington Children's Safe Products Act	http://apps.leg.wa.gov/RCW/default.aspx?cite=70.240
Washington	Occupational Health	Washington Department of Labor & Industries SHARP Publications	http://www.lni.wa.gov/Safety/Research/Pubs/default.asp
West Virginia	Environment	West Virginia Department of Environmental Protection	www.dep.wv.gov
West Virginia	Environmental Health/Health	West Virginia Department Health & Human Services | Bureau for Public Health	www.dhhr.wv.gov/bph
Wisconsin	Environment	Wisconsin Department of Natural Resources	www.dnr.wi.gov
Wisconsin	Environmental Health/Health	Wisconsin Department of Health Services	www.dhs.wisconsin.gov/environmental/
Wisconsin	Occupational Health	Wisconsin Department of Health Services | Wisconsin Occupational Health Program	www.dhs.wisconsin.gov/occupational-health/
Wyoming	Environment	Wyoming Department of Environmental Quality	http://deq.wyoming.gov/
Wyoming	Environmental Health/Health	Wyoming Department of Health	https://health.wyo.gov/
Wyoming	Occupational Health	Wyoming Departmetn of Workforce Services | OSHA	www.wyomingworkforce.org/businesses/osha/
All	TSCA	National Conference of State Legislatures (NCSL) | Toxic Substance Control Act Reform	http://www.ncsl.org/research/environment-and-natural-resources/state-chemical-statutes.aspx

Appendix B

PROQUEST DIALOG™ DATABASE LIST

AN A-Z LIST OF ALL DATABASES AVAILABLE ON PROQUEST DIALOG

A

ABI/INFORM® Professional Advanced
ABI/INFORM Professional Advanced is a multidisciplinary business research database including around 5,500 full text scholarly journals, trade magazines, newsletters and other business resources. The title list is actively managed and the archive goes back to 1971.

ABI/INFORM® Professional Market Research
ABI/INFORM Professional Market Research offers a premium collection of market research reports and market news services, covering country economics and growth forecasts, economic and trade datasets, global industries and market analysis, and company information.

Abstracts in New Technology & Engineering
ANTE contains a comprehensive index to world literature on technological and engineering innovations dating back to 1971 with a specific focus on U.S. patents.

Adis Clinical Trials Insight
Adis Clinical Trials Insight covers the progress of global clinical trials as they are planned, recruited and conducted, and provides rapid digest summaries of best-evidence study results as they are presented or published. Data is sourced from top clinical meetings, significant publications in the leading medical journals, trial registry websites, and information from media releases.

Adis Pharmacoeconomics & Outcomes News
Adis PharmacoEconomics & Outcomes News provides up-to-date analyses and news on world pharmacoeconomics and healthcare outcomes news, views, and practical applications.

Adis R&D Insight
Adis R&D Insight is a drug pipeline database that tracks and evaluates drugs worldwide through the entire development process, from discovery through pre-clinical and clinical studies to launch. Information is sourced from company contacts, press releases, international conferences, company websites, and medical journals.

Adis Reactions
Adis Reactions provides summaries of the world's adverse drug reaction news and published adverse drug reaction case reports, including labelling changes, drug withdrawals due to safety issues, adverse reaction research and current issues in drug safety. Content is sourced from journals, scientific meetings, media releases, regulatory agency websites, and bulletins from the National Centers that participate in the WHO International Drug Monitoring Programme.

AGRICOLA Professional
AGRICOLA provides extensive bibliographic coverage of worldwide literature citations related to all aspects of agriculture.

PROQUEST DIALOG DATABASE LIST

AGRIS
AGRIS is the international information system for agricultural science and technology.

Allied & Complementary Medicine™
Allied & Complementary Medicine covers the fields of complementary or alternative medicine and allied health.

Aluminium Industry Abstracts
Aluminium Industry Abstracts is a comprehensive index to world literature on aluminium/aluminum production processes, products, applications and business developments.

Analytical Abstracts
Analytical Abstracts covers all aspects of analytical chemistry.

Aqualine
Aqualine focuses on trade, technical and scientific literature concerning all aspects of water resources.

Aquatic Science and Fisheries Abstracts (ASFA)
ASFA covers aquatic resources in serial publications, books, reports, conference proceedings, translations and limited-distribution literature.

Argentina Patents Fulltext
Argentina Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

Austria Patents Fulltext
Austria Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

Australian Education Index
The Australian Education Index is a comprehensive collection of educational research documents relating to educational trends, policy, and practices. Coverage includes trends and practices in teaching, learning and educational management.

Australia Patents Fulltext
Australia Patents Fulltext contains bibliographic data, full text, front page image, legal status, patent families and links to PDFs.

B

Belgium Patents Fulltext
Belgium Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

BIOSIS Previews®
Biosis Previews covers every area of the life sciences including agriculture, biodiversity, biotechnology, clinical and experimental medicine, drug discovery, gene therapy, marine biology, nutrition, parasitology, pharmacology, toxicology and many other topics back to the early 20th century. Abstracts are provided from over 5,200 journals as well as meetings, books and reports, worldwide.

BIOSIS® Toxicology
BIOSIS Toxicology contains citations from BIOSIS that focus on toxicology and related topics.

Brazil Patents Fulltext
Brazil Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

British Library Inside Conferences
British Library Inside Conferences contains details of papers given at congresses, symposiums, conferences, expositions, workshops, and meetings received at the British Library Document Supply Centre.

British Nursing Index
British Nursing Index is a leading database for the support of practice, education, research, and development for nurses, midwives, health visitors, and healthcare assistants working in the UK or following UK practice.

Business & Industry™
Business & Industry contains facts, figures and key events dealing with companies, industries and markets at an international level. With an archive back to 1994, selective content from 2,200 journal titles in total is available. Most records are available in full text.

PROQUEST DIALOG DATABASE LIST

C

CAB ABSTRACTS
CAB Abstracts covers the worldwide literature of the applied life sciences, including agriculture, environment, veterinary sciences, applied economics, food science, public health and nutrition back to the early 20th century. Articles are selected from over 10,000 serials, books and conference proceedings.

Canada Patents Fulltext
Canada Patents Fulltext contains bibliographic data, full text, front page image, legal status, patent families and links to PDFs.

Ceramic Abstracts
Ceramic Abstracts covers manufacturing, processing, applications, properties and testing of traditional and advanced ceramics in journal articles, conference proceedings, technical reports, trade journal/ newsletter items, patents, books and press releases.

Chemical Business NewsBase
Chemical Business NewsBase contains facts, figures, news, views and comments on the chemical industry and its allied end-use sectors worldwide.

Chemical Engineering & Biotechnology Abstracts
Chemical Engineering & Biotechnology Abstracts provides comprehensive information aimed specifically at chemical and process engineers or biotechnologists. Coverage includes the theory of chemical processing and laboratory experimentation to evaluate theories or to provide data, industrial practice, economics, equipment, instrumentation, corrosion studies and prevention, environmental and personal safety factors.

Chemical Safety NewsBase
Chemical Safety NewsBase contains information on the hazardous effects of chemicals and processes encountered by workers in industry and laboratories.

China Patents Fulltext
China Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

Civil Engineering Abstracts
Civil Engineering Abstracts covers architecture, construction, structural (including earthquake/ seismic) design, transportation systems, and surveying literature from scholarly and trade journals, conference papers, magazines, books, patents and technical reports.

Computer & Information Systems Abstracts
Computer & Information Systems Abstracts provides access to the worldwide literature on the latest theoretical research and practical applications in the field of computer science and information systems technology.

Corrosion Abstracts
Corrosion Abstracts is an index to world literature on corrosion science and engineering, corrosion characteristics, preventive measures, materials, construction, and performance and equipment for many industries.

Current Contents Search®
Current Contents provides full bibliographic coverage of articles in every leading journal in the sciences, social sciences, arts and humanities worldwide. In addition, it provides the complete table of contents for each journal issue it covers. Over 5,200 international journals are included.

D

Denmark Patents Fulltext
Denmark Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

Derwent Chemistry Resource
The Derwent Chemistry Resource contains chemical substance information for the chemicals within Derwent World Patents Index® and the Derwent Drug File.

PROQUEST DIALOG DATABASE LIST

Derwent Drug File
Derwent Drug file presents a unique combination of chemical and biological information from the worldwide pharmaceutical literature covering all aspects of drug development, synthesis, evaluation, manufacture and use. Over 1,200 journals, as well as conference proceedings and meeting reports, are covered.

Derwent Drug Registry
The Derwent Drug Registry provides the capability for retrieving groups of drugs that have common structural features and/or biological activities.

Derwent World Patents Index®
The Derwent World Patents Index provides patent family records that contain bibliographic data, Thomson Reuters-assigned titles and abstracts, numerous patent indexing systems, and drawings.

DH-DATA: Health Administration, Medical Toxicology & Environmental Health
DH-Data covers core subjects in the United Kingdom, including health service/hospital administration and medical toxicology/environmental health.

Drug Information Fulltext
Drug Information Fulltext provides complete evaluative drug descriptions on thousands of drug products available in the U.S.

E

Earthquake Engineering Abstracts
Earthquake Engineering Abstracts covers seismic phenomena, geology, and civil infrastructure from journal articles, conferences and books.

Ei Compendex®
Ei Compendex is the most comprehensive bibliographic engineering database, covering 190 disciplines from the world's significant engineering and technology literature. It covers over 3,700 journals as well as monograph literature and contains records dating back to the early 19th century.

Ei EnCompassLit™
Ei EnCompassLit contains comprehensive coverage of petroleum, petrochemical, natural gas and energy-related industries.

Electronics and Communications Abstracts
Electronics and Communications Abstracts covers circuits, photonics, telecommunications equipment and instrumentation, power systems, and electrical engineering from journal articles.

Embase®
Embase is a leading international biomedical database, providing information on all aspects of human medicine and related disciplines with an emphasis on drugs - from pre-clinical studies to critical toxicology and safety. Over 7,600 journals are covered, including all of those covered by Medline and 2,000 not covered by Medline. Embase also covers 2,500+ conferences.

Embase® Alert
Embase Alert provides access to the latest eight weeks of biomedical and drug research literature, prior to entry into Embase itself.

EMCare®
EMCare, produced by Elsevier, covers all nursing specialties and nursing healthcare professions.

Energy Science and Technology
Energy Science and Technology contains worldwide references to basic and applied sci-tech research literature.

Engineered Materials Abstracts
Engineered Materials Abstracts is an index to world literature on engineered materials such as polymers, plastics, rubber, ceramics and composites and addresses manufacturing practices, properties and applications of these materials.

Environmental Engineering Abstracts
Environmental Engineering Abstracts covers technological and engineering aspects of air and water quality, environmental safety and energy production from journal articles.

PROQUEST DIALOG DATABASE LIST

ERIC
ERIC is sponsored by the U.S. Department of Education to provide extensive access to education-related literature. ERIC provides coverage of journal articles, conferences, meetings, government documents, theses, dissertations, reports, audiovisual media, bibliographies, directories, books and monographs.

ESPICOM Pharmaceutical & Medical Device News
Espicom Pharmaceutical & Medical Device News provides current news and developments on companies and markets in the pharmaceutical and medical device industries worldwide.

Eurasia Patents Fulltext
Eurasia Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

European Patents Fulltext
European Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

F

FDAnews
FDAnews provides both U.S. and international regulatory, legislative, and business news and information for companies and organizations that are regulated by the FDA and the European commission.

Finland Patents Fulltext
Finland Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

FLUIDEX (Fluid Engineering Abstracts)
FLUIDEX covers the global trade and scientific literature in the use, control and management of fluids for engineering applications.

Foodline®: MARKET
Foodline: Market provides detailed analyses of international food and drinks markets.

Foodline®: PRODUCT
Foodline: Product monitors new food and drink products launched worldwide.

Foodline®: SCIENCE
Foodline: Science covers international scientific and technical information on the food and drinks industry.

FSTA
FSTA is a comprehensive source of worldwide information on food science, food technology and food-related human nutrition.

France Patents Fulltext
France Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

G

Gale Group Computer Database™
Gale Group Computer Database provides comprehensive information about the computer, electronics, and telecommunications industries.

Gale Group Health Periodicals Database
Gale Group Health Periodicals Database provides both general interest-related and key technical resources in the medical field.

Gale Group New Product Announcements/Plus®
Gale New Product Announcements/Plus contains the full text of press releases from all industries covering announcements related to products, with a focus on new products and services.

Gale Group Newsletter Database™
Gale Group Newsletter Database contains the full text of specialized industry newsletters.

Gale Group PharmaBiomed Business Journals
Gale Group PharmaBiomed Business Journals database provides international coverage of full-text articles from trade journals on pharmaceuticals, biotechnology and healthcare.

PROQUEST DIALOG DATABASE LIST

Gale Group PROMT®
Gale Group PROMT is a multi-industry database providing broad, international coverage of companies, products, markets and applied technologies for a wide range of industries and services. The archive goes back to 1972, with selective coverage from some 3,500 journals. The full text is available for most records, and the database employs Gale's highly respected subject indexing to enable effective retrieval of relevant information.

Gale Group Trade & Industry Database™
Gale Group Trade & Industry Database is a multi-industry database covering international company, industry, product, and market information. Over 4,300 titles with selected coverage are available with an archive stretching back to 1976. The database contains a mixture of full text, abstracted, and citation-only records; some 50% of records are available in full text.

GEOBASE™
GEOBASE provides bibliographic information and abstracts for development studies, the Earth sciences, ecology, geomechanics, human geography, and oceanography.

GeoRef
GeoRef covers geosciences, geochemistry, and geophysics from journal articles, books, maps, conference papers, reports and theses.

Germany Patents Fulltext
Germany Patents Fulltext (DE and DD patents) contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

Global Health
Global Health covers core health journals as well as sources not routinely indexed by major medical databases. It provides deep subject coverage of information relating to human health and communicable diseases.

Global Patents Bibliographic
The Global Patents Bibliographic database contains bibliographic data for patents from 69 countries, and links to PDFs.

Great Britain Patents Fulltext
Great Britain Patents Fulltext contains full text, bibliographic data, front page image, legal status, patent families and links to PDFs.

H

HSELINE: Health and Safety
HSELINE is produced by the United Kingdom Health and Safety Executive (HSE) Library and Information Services. This database includes all aspects of health and safety at work.

I

ICONDA – International Construction Database
ICONDA covers worldwide technical literature on civil engineering, urban and regional planning, architecture, and construction.

IFI Claims US Patents and Legal Status
IFI CLAIMS US Patents and Legal Status contain bibliographic data, full text, citations and legal status for U.S. patents. Value-add enhancements include standardized assignees, in-depth legal status, enhanced subject indexing and classification code descriptions.

IMS Company Profiles
IMS Company Profiles examines annually the internal make-up of key pharmaceutical companies worldwide. Each profile analyzes the critical components of a pharmaceutical company, providing an assessment of the company's business strategy.

IMS New Product Focus
IMS New Product Focus tracks worldwide pharmaceutical product launches, records the very first launch of a product in a particular country and identifies the indication and price (when available) at the time of the initial launch.

PROQUEST DIALOG DATABASE LIST

IMS Patent Focus
IMS Patent Focus contains patent family and substance information for marketed and Phase III clinical trials drugs.

IMS Pharma Trademarks
IMS Pharma Trademarks provides the latest product information on launched drugs worldwide, including sales information.

IMS R&D Focus
IMS R&D Focus is a drug pipeline database that tracks and evaluates drugs worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to launch. Licensing availability and patent summary information is included. Information is sourced from journals, conferences and news releases as well as from pharmaceutical companies directly.

IMS R&D Focus Drug News
IMS R&D Focus Drug News covers the latest developments in international pharmaceutical research and development.

Incidence & Prevalence Database
The Incidence & Prevalence database provides disease and epidemiology related information, statistics and sources for various regions of the world.

India Patents Fulltext
India Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, and links to PDFs.

INPADOC/Family and Legal Status
INPADOC/Family and Legal Status contains bibliographic data, abstract, legal status and patent family information from 99 patent authorities.

Inspec®
Inspec, a bibliographic database, is a major source of worldwide literature on physics, electrical and electronic engineering, computer and control engineering, information technology and mechanical, manufacturing and production engineering. The database has a deep archive back to 1898 and includes nearly 5,000 scientific and technical journals (1,600 of which are indexed from cover to cover), some 2,500 conference proceedings, as well as numerous books, reports, dissertations and scientific videos.

International Pharmaceutical Abstracts
International Pharmaceutical Abstracts Database provides comprehensive coverage of worldwide pharmaceutical literature.

Ireland Patents Fulltext
Ireland Patents Fulltext contains bibliographic data, full text, front page image, legal status, patent families and links to PDFs.

Italy Patents Fulltext
Italy Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

J

Jane's Defense & Aerospace News/Analysis
Jane's Defense & Aerospace News/Analysis provides global news and analysis covering the defense and aerospace markets.

Japan Patents Fulltext
Japan Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

Japio – Patent Abstracts of Japan
JAPIO contains bibliographic data and English language abstracts for Japanese unexamined patent applications.

PROQUEST DIALOG DATABASE LIST

K

King's Fund
King's Fund covers policy and management of health and social care services in the United Kingdom.

Korea Patents Fulltext
Korea Patents Fulltext contains bibliographic data, full text, English machine translations, front page image, legal status, patent families and links to PDFs.

KOSMET: Cosmetic Science
KOSMET: Cosmetic Science covers information on cosmetic and perfume science and technology, specifically dealing with raw materials, manufacture, analysis, control and use.

L

Lancet Titles
Lancet titles contain health and medicine journal articles.

LitAlert®
LitAlert® contains patent and trademark infringement lawsuits filed in the 94 U.S. District Courts.

Luxembourg Patents Fulltext
Luxembourg Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

M

Material Safety Data Sheets – OHS™
Material Safety Data Sheets is a comprehensive collection of material safety data sheets on more than 50,000 chemicals, including pure substances and mixtures.

Materials Business File
Materials Business File covers materials science, engineering, aerospace, plant development and construction, government regulations and management issues from journal articles.

Mechanical & Transportation Engineering Abstracts
Mechanical & Transportation Engineering Abstracts covers automotive engineering, naval and marine engineering, aerospace engineering, and industrial and manufacturing engineering.

MEDLINE®
MEDLINE is the US National Library of Medicine's premier bibliographic database containing journal articles in life sciences with a concentration on biomedicine and health, including clinical and experimental medicine, dentistry, nursing, pharmacology, veterinary medicine, psychiatry and psychology, toxicology and many other related fields. About 5,600 international journals are covered.

METADEX
METADEX covers processing, properties, testing, analysis and applications of non-ferrous metals, steels, alloys, compounds and metal matrix composites.

Meteorological and Geoastrophysical Abstracts
Meteorological and Geoastrophysical Abstracts cover meteorology, climatology, hydrology, glaciology from journal articles, conference proceedings, books and technical reports.

Mexico Patents Fulltext
Mexico Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

Monaco Patents Fulltext
Monaco Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

N

Netherlands Patents Fulltext
Netherlands Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

PROQUEST DIALOG DATABASE LIST

New England Journal of Medicine
The New England Journal of Medicine contains full-text articles excluding meeting notices, "Books Received," and advertising content.

Norway Patents Fulltext
Norway Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

NTIS: National Technical Information Service
NTIS is the preeminent resource for accessing the latest research sponsored by the United States and select foreign governments. It covers reports, journal articles, data files, computer programs and audio/visual products.

O

Oceanic Abstracts
Oceanic Abstracts focuses exclusively on worldwide technical literature pertaining to the marine and brackish-water environments. It covers marine biology and physical oceanography, fisheries, aquaculture, non-living resources, meteorology and geology, plus environmental, technological, and legislative topics.

P

PAIS International
PAIS International covers the full range of the social sciences worldwide with emphasis on contemporary public issues and the making and evaluating of public policy.

Paperbase
Paperbase includes information on all aspects of the pulp, paper and nonwovens industries, from raw materials to finished products.

PAPERCHEM
PAPERCHEM covers the international patent and journal literature related to pulp and paper technology.

PASCAL
PASCAL covers the world's science, social science, technology and medical literature with special emphasis on European sources. Conference proceedings, dissertations, books, patents and reports are covered, in addition to over 3,000 journals.

Patents Citation Index®
Derwent Patents Citation Index contains patent and literature citations for DWPI patent families.

PIRABASE
PIRA (Packaging, Paper, Printing and Publishing, Imaging and Nonwovens Abstracts) covers worldwide literature and patents on the pulp and paper, packaging, printing, publishing, imaging and nonwovens industries.

Pollution Abstracts
Pollution Abstracts combines government policy and scientific research into air pollution, marine pollution, and waste management from journal articles, conference proceedings and other sources.

Polymer Library
RAPRA Polymer Library (formerly known as RAPRA: Rubber and Plastics) is dedicated exclusively to rubbers, plastics, adhesives, and polymeric composites.

Portugal Patents Fulltext
Portugal Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

ProQuest Advanced Tech & Aerospace Professional
ProQuest Advanced Tech & Aerospace Professional includes access to more than 3,000 periodicals across diverse high-tech and aerospace domains, from communications and navigation to acoustics and plasmas. Includes data from four specialist databases.

PROQUEST DIALOG DATABASE LIST

ProQuest Biological & Health Science Professional
ProQuest Biological & Health Science Professional is a premium biological research resource, covering human, animal and plant science. It includes data from 26 specialist databases covering diverse subjects such as genetics and oncogenes, health and safety, immunology, neuroscience, chemoreception and molecular biology.

ProQuest Dissertations & Theses Professional
ProQuest Dissertations & Theses Professional is world's most comprehensive collection of dissertations and theses, and is the official digital dissertations archive for the Library of Congress and the database of record for graduate research. Some 3 million dissertations and theses are available, of which approximately half are available in full text.

ProQuest Environmental Science Professional
ProQuest Environmental Science Professional provides unparalleled and comprehensive coverage of the environmental sciences. Abstracts and citations are drawn from a compilation of 19 diverse databases and over 6,000 serials including scientific journals, conference proceedings, reports, monographs, books and government publications.

ProQuest Materials Research Professional
ProQuest Materials Research Professional provides bibliographic coverage of serial and non-serial literature on metallurgy, ceramics, polymers, and composites used in engineering applications. It includes data from seven specialist materials databases.

ProQuest Newsstand™ Professional
ProQuest Newsstand Professional is a collection of leading newspapers, magazines and wire services with geographic reach throughout the United States and around the world. The 2,400 titles available are actively managed and the database has coverage back to 1983.

ProQuest Technology Research Professional
ProQuest Technology Research Professional is the most comprehensive engineering and technology research offering from ProQuest, with coverage of the world literature on technology and applied science, including materials science, aerospace engineering, mechanical engineering, civil engineering, condensed matter physics, computer science and electronic engineering. Information is drawn from scholarly journals, conferences, patents and other source publications.

PsycINFO
PsycINFO provides international bibliographic coverage of the literature in the behavioral sciences and mental health, reaching beyond psychology to related disciplines like medicine, law, social work, neuroscience, business, nursing, forensics, engineering and more. Books and dissertations as well as almost 2,500 journals are covered.

R

Registry of Toxic Effects of Chemical Substances (RTECS®)
RTECS is a comprehensive database of toxic information for more than 100,000 chemical substances.

Russia Patents Fulltext
Russia Patents Fulltext (RU and SU patents) contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

S

SciSearch®: a Cited Reference Science Database
SciSearch is a major international database of science, technology, biomedicine and related disciplines. Unlike other sources, SciSearch includes each article's cited references in addition to the usual bibliographic data. Over 5,200 journals are covered.

PROQUEST DIALOG DATABASE LIST

Social SciSearch®
Social SciSearch® is an international, multidisciplinary index to the literature of the social, behavioral and related sciences.

Solid State and Superconductivity Abstracts
This database covers applied physics, and information relating solid state applications, superconductors, semiconductors from mainly journal articles.

Spain Patents Fulltext
Spain Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

Sweden Patents Fulltext
Sweden Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

Switzerland Patents Fulltext
Switzerland Patents Fulltext contains bibliographic, full text, English machine translation, front page image, legal status, patent families and links to PDFs.

T

Thomson Reuters Embargoed Research Collection®
Thomson Reuters Embargoed Research Collection offers premium market research reports on companies, industries and topics written by analysts at leading investment banks, brokerage houses and consulting firms worldwide. Reports are full-text searchable, with citations and tables of contents providing access to report sections or complete reports.

Toxfile®
Toxfile contains citations from Medline that cover the toxicological, pharmacological, biochemical and physiological effects of drugs, pesticides and other chemicals.

Transport Research International Documentation (TRID)
TRID is a composition file including aspects of air, highway, rail, maritime and waterborne transport, mass transit, and other transportation modes.

TULSA™ (Petroleum Abstracts)
TULSA (Petroleum Abstracts) provides bibliographic citations to articles, patents, meeting papers, and government reports of interest to both scientists and technical professionals.

U

UBM Computer Fulltext
UBM Computer Full Text contains a variety of important computer, communications and electronics trade magazines in full text from UBM LLC.

United States Patents Fulltext
United States Patents Fulltext contains bibliographic data, full text, front page image, legal status and links to PDFs for U.S.-granted patents and published applications.

W

Water Resources Abstracts
Water Resources Abstracts covers water resources, water and wastewater treatment, and water pollution issues from journal articles, books, conference proceedings and technical reports.

Weldasearch®
Weldasearch is a database of short abstracts of articles on welding, joining, and allied technologies.

WIPO PCT Patents Fulltext
WIPO Patents Fulltext contains bibliographic data, full text, English machine translation, front page image, legal status, patent families and links to PDFs for Patent Cooperation Treaty applications.

Z

Zoological Record Plus®
Zoological Record Plus is a comprehensive index to zoological and animal science literature.

Appendix C

Databases Typically Used on STN®

Chemical Abstracts
Coverage 1907-current
- Analytical chemistry
- Applied chemistry
- Biochemistry
- Chemical engineering
- Macromolecular chemistry
- Organic chemistry

Sources
- Journals: thousands of journals monitored
- Patents
- Conference Proceedings
- Electronic-only Journals
- Books
- Dissertations
- Reviews
- Technical Disclosures
- Web Pre-prints
- Meeting Abstracts

Chemical Abstracts Reactions
Coverage 1840-current
CASREACT covers synthetic organic research, including organometallics, total syntheses of natural products, and biotransformation reactions.

Chemical Catalogs Online
Only current catalogs
- Business
- Chemistry
- Manufacturers

Regulated Chemicals Listing (Directory)
Coverage 1980-current
- Substance identity information, inventory status, source of information, and summaries of regulatory activity, reports, and other compliance information
- CHEMLIST offers the convenience of identifying—in one place—the regulatory requirements for a specific substance from many of the world's most significant regulated substances lists.

DOE ENERGY
Coverage 1974-2013 (closed file)
- Electric power generation and transmission
- Energy conservation
- Energy consumption and utilization

- Energy conversion and storage
- Energy policy, management, economy
- Energy-related aspects of environmental and biomedical sciences, health, safety, physics, esp. elementary particles, nuclear physics, accelerators, chemistry, materials, geosciences
- Fossil fuels (coal, petroleum, natural gas, etc.)
- Fusion energy
- Hydrogen and other natural and synthetic fuels
- Nuclear energy (fuels, power plants, technology)
- Renewable energies (solar, wind, geothermal, etc.)

Elsevier BIOBASE

Coverage 1994–current

- Applied microbiology and biotechnology
- Cancer research
- Cell and developmental biology
- Clinical chemistry
- Ecological and environmental sciences
- Endocrinology and metabolism
- Genetics and molecular biology
- Neuroscience
- Plant science
- Protein biochemistry
- Toxicology

Inorganic Crystal Structure Database (ICSD)

Coverage 1913–current

- Crystal structures of inorganic compounds
- Physical chemistry
- Physical properties
- Crystallography
- Physics
- Inorganic chemistry
- Property data
- Materials science
- Thermal properties
- Phase transitions

Cosmetic & Perfume Science and Technology

Coverage 1968-current

- Active ingredients
- Manufacture
- Analysis
- Packaging
- Biological properties
- Physiochemical properties

- Clinical studies
- Product development
- Cosmetic and perfume science and technology
- Research and development of raw materials
- Formulations
- Safety
- Knowledge of healthy skin and its adnexa (hair, nails, teeth, glands)
- Trading of perfumes and cosmetics

Natural Products Alert

Coverage 1650-2011 (closed file)

- Approximately 50% of the file is from systematic survey of the literature from 1975 to 2011. The remaining records were obtained by *selective retrospective indexing dating back to 1650.*
- NAPRALERT (NAtural PRoducts ALERT) contains bibliographic and factual data on natural products, including information on the pharmacology, biological activity, taxonomic distribution, chemistry of plant, microbial, and animal (including marine) extracts as well as ethnomedicine use records. In addition, the database contains information on the chemistry and pharmacology of secondary metabolites that are derived from natural sources and that have known structure.
- The records in this file contain bibliographic information and factual data on natural products, including CAS Registry Numbers for many chemical constituents.

Toxicology Center (TOXCENTER)

Coverage 1907–current

- Adverse Drug Reactions
- Air Pollution
- Animal Venom
- Antidotes
- Carcinogenesis via Chemicals
- Chemically Induced Diseases
- Drug Evaluations
- Environmental Pollution
- Food Contamination
- Mutagenesis
- Occupational Hazards
- Pesticides and Herbicides
- Radiation Teratology
- Toxicological Analysis
- Waste Disposal

Appendix D

Appendix D. Search terms for Human Health Hazard Information

The following terms will be used, in conjunction with CASRN and chemical name(s), to search PubMed:

((DNA[tiab] AND breaks[tiab]) OR absorption[tiab] OR absorption[mh] OR activate[tiab] OR activated[tiab] OR acute[tiab] OR adverse[tiab] OR adverse-effects[sh] OR Ames-assay[tiab] OR Ames-test[tiab] OR animal[tiab] OR blood[tiab] OR blood[mh] OR brain[mh] OR brain[tiab] OR cancer[tiab] OR carcinogen[tiab] OR carcinogenesis[tiab] OR carcinogenic[tiab] OR carcinogenicity[tiab] OR carcinogens[tiab] OR carcinogens[mh] OR cardiac[tiab] OR case-control[tiab] OR case-control-studies[mh] OR case-referent[tiab] OR case-report[tiab] OR case-reports[tiab] OR case-reports[pt] OR cell[tiab] OR cell-proliferation[mh] OR cells[tiab] OR cells[mh] OR chemokine[tiab] OR chemokines[tiab] OR chromosomal-aberration[tiab] OR chromosomal-aberration[tiab] OR chromosomal-aberrations[tiab] OR chromosomal-aberrations[mh] OR chronic[tiab] OR cognitive[tiab] OR cohort[tiab] OR cohort-studies[mh] OR congenital-abnormalities[mh] OR corrosion[mh] OR corrosion[tiab] OR crosslink[tiab] OR cytogenicity[tiab] OR cytokine[tiab] OR cytokines[tiab] OR cytokines[mh] OR cytotoxic[tiab] OR cytotoxicity[tiab] OR dam[tiab] OR dams[tiab] OR death[mh] OR death[tiab] OR dermal[tiab] OR detoxification[tiab] OR detoxify[tiab] OR development[tiab] OR developmental[tiab] OR diet[mh] OR diet[tiab] OR dietary[tiab] OR diets[tiab] OR distribution[tiab] OR DNA-adduct[tiab] OR DNA-adducts[mh] OR DNA-adducts[tiab] OR DNA-breaks[mh] OR DNA-damage[mh] OR DNA-damage[tiab] OR DNA-repair[mh] OR DNA-repair[tiab] OR dog[tiab] OR dogs[tiab] OR dogs[mh] OR dose[tiab] OR drinking-water[tiab] OR drinking-water[mh] OR eliminate[tiab] OR elimination[tiab] OR embryo[tiab] OR embryonic[tiab] OR embryos[tiab] OR employee[tiab] OR employees[tiab] OR endocrine[tiab] OR endpoint[tiab] OR endpoints[tiab] OR enteral-nutrition[mh] OR epidemiologic[tiab] OR epidemiological[tiab] OR epidemiology[mh] OR epidemiology[sh] OR epidemiology[tiab] OR epigenetic[tiab] OR epigenetics[tiab] OR epigenomics[tiab] OR epigenomics[mh] OR female[tiab] OR females[tiab] OR fetal[tiab] OR fetus[tiab] OR fetus[mh] OR fetuses[tiab] OR gavage[tiab] OR Gene[tiab] OR gene- expression[mh] OR genes[tiab] OR genes[mh] OR genetic[tiab] OR genetics[tiab] OR genotoxic[tiab] OR genotoxicity[tiab] OR germ-line-mutation[tiab] OR germ-line-mutation[mh] OR growth-and-development[mh] OR guinea-pig[tiab] OR guinea-pigs[tiab] OR guinea-pigs[mh] OR hamster[tiab] OR hamsters[tiab] OR hazard[tiab] OR heart[tiab] OR heart[mh] OR hemotoxic[tiab] OR hemotoxicity[tiab] OR hemotoxin[tiab] OR hemotoxins[tiab] OR hepatic[tiab] OR hepatotoxic[tiab] OR hepatotoxicity[tiab] OR hepatotoxin[tiab] OR hepatotoxins[tiab] OR human[tiab] OR humans[tiab] OR humans[mh] OR immunotoxic[tiab] OR immunotoxicity[tiab] OR immunotoxin[tiab] OR immunotoxins[tiab] OR immunotoxins[mh] OR incidence[tiab] OR incidences[tiab] OR individual[tiab] OR individuals[tiab] OR inflammation[tiab] OR inflammation[mh] OR inflammatory[tiab] OR inhalation[tiab] OR inhalation[mh] OR inhale[tiab] OR inhaled[tiab] OR inhibit[tiab] OR inhibited[tiab] OR inhibitory[tiab] OR interact[tiab] OR interacted[tiab] OR interaction[tiab] OR intestine[tiab] OR intestines[tiab] OR intestines[mh] OR in-vitro[tiab] OR in-vitro-techniques[mh] OR in-vivo[tiab] OR irritation[tiab] OR kidney[tiab] OR kidney[mh] OR LC50[tiab] OR LD50[tiab] OR lethal-concentration-50[tiab] OR Lethal-Dose-50[tiab] OR Lethal-Dose-50[mh] OR litter[tiab] OR litters[tiab] OR liver[tiab] OR liver[mh] OR LOAEC[tiab] OR LOAEL[tiab] OR LOEL[tiab] OR longitudinal[tiab] OR long-term-adverse-effects[mh] OR lung[tiab] OR lung[mh] OR male[tiab] OR malformation[tiab] OR malformations[tiab] OR malformed[tiab] OR malignancies[tiab] OR malignancy[tiab] OR malignant[tiab] OR margin-of-exposure[tiab] OR maternal[tiab] OR mechanism[tiab] OR mechanisms[tiab] OR mechanistic[tiab] OR metabolism[tiab] OR metabolism[mh] OR metabolism[sh] OR metastasis[tiab] OR metastasize[tiab] OR metastatic[tiab] OR mg/kg/day[tiab] OR mg/kg-bw/day[tiab] OR mg/L[tiab] OR mg/m3[tiab] OR mg-kg/day[tiab] OR mice[mh] OR mice[tiab] OR micronuclei[tiab] OR micronucleus[tiab] OR mode-of-action[tiab] OR monkey[tiab] OR monkeys[tiab] OR mortality[mh] OR mortality[tiab] OR mouse[tiab] OR mouth[tiab] OR mouth[mh] OR mutagen[tiab] OR mutagenesis[tiab] OR mutagenic[tiab] OR mutagens[mh] OR mutagens[tiab] OR mutation[tiab] OR mutation[mh] OR nasal[tiab] OR neoplasm[tiab] OR neoplasms[tiab] OR neoplasms[mh] OR neoplastic[tiab] OR nephrotoxic[tiab] OR nephrotoxicity[tiab] OR nephrotoxin[tiab] OR nephrotoxins[tiab] OR nested[tiab] OR neurobehavior[tiab] OR neurobehavioral[tiab] OR neurologic[tiab] OR neurological[tiab] OR neurophysiological[tiab] OR neuropsychological[tiab] OR neurotoxic[tiab] OR neurotoxicity[tiab] OR neurotoxin[tiab] OR neurotoxins[tiab] OR neurotoxins[mh] OR NOAEC[tiab] OR NOAEL[tiab] OR NOEL[tiab] OR nonmalignant[tiab] OR nonneoplastic[tiab] OR nose[tiab] OR nose[mh] OR OECD-Test-Guideline[tiab] OR OECD-Test-Guidelines[tiab] OR oncogene[tiab] OR oncogenes[tiab] OR oncogenes[mh] OR

oncogenesis[tiab] OR oral[tiab] OR organ[tiab] OR organs[tiab] OR ototoxic[tiab] OR ototoxicity[tiab] OR oxidative-damage[tiab] OR oxidative-stress[tiab] OR oxidative-stress[mh] OR participant[tiab] OR participants[tiab] OR paternal[tiab] OR PBPK[tiab] OR people[tiab] OR perinatal[tiab] OR person[tiab] OR pharmacodynamic[tiab] OR pharmacodynamics[tiab] OR pharmacokinetic[tiab] OR pharmacokinetics[mh] OR pharmacokinetics[tiab] OR pharmacokinetics[sh] OR pharmacology[sh] OR pharmacology[mh] OR pharmacology[tiab] OR polyploid[tiab] OR polyploidy[tiab] OR polyploidy[mh] OR postnatal[tiab] OR pregnancy[mh] OR pregnancy[tiab] OR pregnancy-complications[mh] OR pregnant[tiab] OR prenatal[tiab] OR prevalence[tiab] OR prevalent[tiab] OR promote[tiab] OR promotion[tiab] OR pulmonary[tiab] OR rabbit[tiab] OR rabbits[tiab] OR rabbits[mh] OR rat[tiab] OR rats[mh] OR rats[tiab] OR registries[mh] OR registries[tiab] OR registry[tiab] OR renal[tiab] OR reproduction[tiab] OR reproduction[mh] OR reproductive[tiab] OR reprotoxic[tiab] OR reprotoxicity[tiab] OR respiration[mh] OR respiration[tiab] OR respiratory[tiab] OR rodent[tiab] OR rodents[tiab] OR SCE[tiab] OR sensitization[tiab] OR sensitized[tiab] OR sensitizer[tiab] OR sensitizing[tiab] OR sister-chromatid-exchange[mh] OR sister-chromatid-exchange[tiab] OR skeletal[tiab] OR skin[tiab] OR skin[mh] OR subchronic[tiab] OR sub-chronic[tiab] OR subject[tiab] OR subjects[tiab] OR systemic[tiab] OR teratogen[tiab] OR teratogenic[tiab] OR teratogens[tiab] OR teratogens[mh] OR toxic[tiab] OR toxicant[tiab] OR toxicants[tiab] OR toxicity[sh] OR Toxicity[tiab] OR Toxicity[sh] OR toxicodynamic[tiab] OR toxicodynamics[tiab] OR toxicokinetic[tiab] OR toxicokinetics[tiab] OR toxicokinetics[mh] OR toxicology[mh] OR toxicology[tiab] OR tumor[tiab] OR tumorigenic[tiab] OR tumors[tiab] OR weight[tiab] OR worker[tiab] OR workers[tiab] OR Adolescen*[tiab] OR Adult*[tiab] OR Age[tiab] OR aged[tiab] OR age-groups[mh] OR ages[tiab] OR Alcohol[tiab] OR At-risk[tiab] OR BMI[tiab] OR body-mass-index[tiab] OR body-mass-index[mh] OR boy[tiab] OR boys[tiab] OR child[tiab] OR children[tiab] OR cigar[tiab] OR Cigarette[tiab] OR cigarettes[tiab] OR cigars[tiab] OR Coexposure[tiab] OR co-exposure[tiab] OR Critical-window*[tiab] OR Diabetes[tiab] OR diabetes-insipidus[mh] OR diabetes-mellitus[mh] OR disadvantaged[tiab] OR Early-life[tiab] OR Elderly[tiab] OR Environmental-justice[tiab] OR Ethanol[tiab] OR Ethnic[tiab] OR ethnic-groups[mh] OR ethnicit*[tiab] OR Females[tiab] OR gastrointestinal-microbiome[mh] OR Gender[tiab] OR Genotype[tiab] OR genotype[mh] OR Genotypes[tiab] OR genotypic[tiab] OR Geriatric[tiab] OR gestation[tiab] OR gestational[tiab] OR girl[tiab] OR girls[tiab] OR Gut[tiab] OR Haplotype[tiab] OR Haplotypes[tiab] OR haplotypes[mh] OR Health-status[mh] OR Health-status[tiab] OR Inequalit*[tiab] OR Inequit*[tiab] OR infancy[tiab] OR infant[tiab] OR OR infants[tiab] OR In- utero[tiab] OR lifestage[tiab] OR Life-stage[tiab] OR lifestages[tiab] OR Life-stages[tiab] OR Males[tiab] OR Men[mh] OR Men[tiab] OR Metagenomic[tiab] OR metagenomics[tiab] OR metagenomics[mh] OR methylation[mh] OR Methylation[tiab] OR Microbiome[tiab] OR Microbiomes[tiab] OR Microbiota[tiab] OR minorities[tiab] OR minorities[tiab] OR Minority[tiab] OR minority-groups[mh] OR Modifying-factor[tiab] OR Modifying-factors[tiab] OR natal[tiab] OR newborn[tiab] OR newborns[tiab] OR Nicotine[tiab] OR nicotine[mh] OR nutritional-status[mh] OR nutritional-status[tiab] OR placenta[mh] OR placenta[tiab] OR placental[tiab] OR Polymorphism[tiab] OR polymorphism,-genetic[mh] OR polymorphisms[tiab] OR poverty[mh] OR Poverty[tiab] OR Preexisting[tiab] OR pre-existing[tiab] OR pregnant-women[mh] OR Preschool[tiab] OR preschooler[tiab] OR preschoolers[tiab] OR Race[tiab] OR Racial[tiab] OR racism[mh] OR racism[tiab] OR Sensitive-population[tiab] OR Sensitive-populations[tiab] OR SES[tiab] OR sex[mh] OR Sex[tiab] OR smoke[tiab] OR Smoke[mh] OR smoker[tiab] OR smokers[tiab] OR smoking[tiab] OR smoking[mh] OR Sociocultural[tiab] OR sociodemographic[tiab] OR Socioeconomic[tiab] OR socio-economic[tiab] OR socioeconomic-factors[mh] OR Susceptibilities[tiab] OR Susceptibility[tiab] OR Susceptible[tiab] OR teenager[tiab] OR teenagers[tiab] OR teens[tiab] OR Tobacco[tiab] OR tobacco-products[mh] OR toddler[tiab] OR toddlers[tiab] OR underserved[tiab] OR Vulnerabilities[tiab] OR Vulnerability[tiab] OR Vulnerable[tiab] OR vulnerable-populations[mh] OR Women[mh] OR Women[tiab] OR cardiovascular[tiab])

Notes: [mh] searched in MeSH field; [tiab] searched in title or abstract fields; [sh] searched in subheading field. Additional terms include: biomonitoring, dopamine, estrogen, progesterone, CAR, PXR.

Appendix B

Reviews of Studies on Physical-Chemical and Environmental Fate Properties

Exponent®

Appendix B

Reviews are presented in the order found in Tables 3-1 through 3-6 in the main text.

Physical-chemical property reviews

Short citation (Author, year, or ID)	**LEI10A**		
Full citation (or link)	**Lei, Y.D., F. Wania, and D. Mathers. 2010. Temperature-dependent vapor pressure of selected cyclic and linear polydimethylsiloxane oligomers. Journal of Chemical & Engineering Data *55*(12): 5868–5873.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	Mixtures of dimethylsiloxane oligomers were obtained from Dow Corning Corporation (Midland, MI).	Was the test substance identified definitively? No	**2**
Composition (purity, origin); single substance (not mixture)	Mixture	Was the source and purity identified? Source was identified, but purity was not.	**3**
Test Design			
Test system	Isothermal retention time of the target compounds were determined using a Perkin-Elmer XL gas chromatographic retention time (GCRT) technique. Essentially, the logarithm of the ratios of the measured GCRTs of the target analytes and a standard reference compound at each temperature are linearly regressed against the logarithm of the vapor pressure of the reference compound; from the slope and intercept, the vapor pressure of the target compound can be derived. This para addressed the overall scope of the p-c and fate summary. Tables 2-4 present the fate information. For this para only: Yellow = new compared to original text.	Were appropriate methods used? Applicable to non-polar compounds such as dimethylsiloxanes.	**1**
Test conditions	determined at temperatures between 308.15 and 438.15) K	Were the test conditions appropriate? Yes	**1**
Methods and Observations			

Short citation (Author, year, or ID)	**LEI10A**		
Full citation (or link)	**Lei, Y.D., F. Wania, and D. Mathers. 2010. Temperature-dependent vapor pressure of selected cyclic and linear polydimethylsiloxane oligomers. Journal of Chemical & Engineering Data *55*(12): 5868–5873.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Analytical or other methods described	Normal alkanes as standard reference and calibration compounds. Standard reference compounds and calibration compounds used.	Was the test substance analytically verified in the test system using appropriate methods? Yes	**1**
Results			
Findings described	124.5 ± 6.2 Pa for D4 vapor pressure at 308.15 -368.15 K	Were the findings consistent with the methodology? Yes	**1**
		Score (6–24):	**9**

Short citation (Author, year, or ID)	**FLANI86A**		
Full citation (or link)	**Flaningam, O.L. 1986. Vapor pressures of poly(dimethylsiloxane) oligomers. J. Chem. Eng. Data 31: 266–272.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	Octamethylcyclotetrasiloxane	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	99% pure as tested in gas chromatography, mix of oligomers provided by Dow	Was the source and purity identified? Yes	**1**
Test Design			
Test system	Use of an ebulliometer.	Were appropriate methods used? Yes	**1**
Test conditions	measured over pressure range of 7 – 133 kPa, approximately 8 measurements on each compound over the range of temperatures.	Were the test conditions appropriate? Yes	**1**
Methods and Observations			
Analytical or other methods described	Multiple oligomers measured over pressure range of 7 – 133 kPa and then fitted to Antoine equation. Extrapolations made based on literature and estimated critical constants, Halm-Stiel extension, of Pifzer's vapor equation. Extrapolated data was found to also fit the AIChE DIPPR vapor pressure equation. Validity of method checked by also measuring water, methylcyclohexane, and diphenyl ether.	Was the test substance analytically verified in the test system using appropriate methods? Yes	**1**
Results			
Findings described	Vapor pressure ranged between 3.36–68 kPa when testing in a range of temperatures 473–578 K	Were the findings consistent with the methodology?	**1**
		Score (6–24):	**6**

Short citation (Author, year, or ID)	**VARAP96A**		
Full citation (or link)	**Varaprath, S., C.L. Frye, and J. Hamelink. 1996. Aqueous solubility of permethylsiloxanes (silicones). Environmental Toxicology and Chemistry *15*(8): 1263-1265.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	Octamethylcyclotetrasiloxane	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	commercially available (Dow Corning Corp., Aldrich Chemical Co., Huls America, etc.);and were distilled only if their purity was less than 99% (not specifically stated for D4)	Was the source and purity identified? Yes	**1**
Test Design			
Test system	Non-turbulent method; 1,500 mL distilled water in 2 L flask with test material added to cover water surface; followed by gentle stirring to avoid cavitation and turbulence.	Were appropriate methods used? Yes	**1**
Test conditions	23 °C, magnetic stir bar	Were the test conditions appropriate? Yes	**1**
Methods and Observations			
Analytical or other methods described	Two analysis methods were used: a purge and trap method connected to a gas-liquid chromatograph column (GLC) and analyzed by GC-MS. Also used GLC following extraction with hexamethyldisiloxane.(MM). Calibration techniques used (methanol plus pure compound)	Was the test substance analytically verified in the test system using appropriate methods? Yes	**1**
Results			
Findings described	From days 21-87, average concentration (by MM extraction and GLC analysis) was 53.1 ± 6.6 ppb and by purge and trap GC-MS 56.2 ± 2.5 ppb	Were the findings consistent with the methodology? Yes	**1**
		Score (6–24):	**6**

Short citation (Author, year, or ID)	**SPRIN89A**		
Full citation (or link)	**Springborn Labporatories, Inc. 1989a. Octamethycyclotetrasiloxane – determination of the water solubility in freshwater. SLI Report # 89-10-3116.**		
Study type (e.g., OECD Guideline if applicable)	**Generator column method (TSCA Test Standard 796.1860)**		
Study Director (if applicable)	**Smith, A.M.**		
GLP Compliance (if applicable)	**Y, with minor exceptions**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	Manufactured by Dow, 99% pure	Was the source and purity identified? Yes	**1**
Test Design			
Test system	A solid support was coated with D4 and ASTM Type II water was pumped through a glass column that contained the coated material. The generator column was directly coupled to a purge and trap liquid sample concentrator Eluted water was analyzed by GC-MS.	Were appropriate methods used? Yes	**1**
Test conditions	After an equilibration period of 32.5 hours, samples were collected at several intervals 13 samples collected between 0 – 291 hours post-equilibration.	Were the test conditions appropriate? Yes no atmospheric exposure occurred – beneficial when testing a highly volatile substance	**1**
Methods and Observations			
Analytical or other methods described	12 measurements were averaged for the final solubility value. Blanks were used. Blank and standard check performed daily.	Was the test substance analytically verified in the test system using appropriate methods? Yes,.	**1**
Results			
Findings described	Water solubility is 74 ± 9.4 µg/L	Were the findings consistent with the methodology? Yes	**1**
		Score (6–24):	**6**

Short citation (Author, year, or ID)	**SPRING89B**		
Full citation (or link)	**Springborn Laboratories, Inc. 1989b. Octamethylcyclotetrasiloxane – determination of the water solubility in synthetic seawater. SLI Report # 89-9-3104.**		
Study type (e.g., OECD Guideline if applicable)	**Generator column method (TSCA Test Standard 796.1860)**		
Study Director (if applicable)	**Smith, A.M.**		
GLP Compliance (if applicable)	**Yes, with minor exceptions noted.**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	Manufactured by Dow, 99% pure	Was the source and purity identified? Yes	**1**
Test Design			
Test system	A solid support was coated with D4 and synthetic seawater was pumped through a glass column that contained the coated material. The generator column was directly coupled to a purge and trap liquid sample concentrator. Eluted water was analyzed by GC-MS. Synthetic seawater was prepared using a documented recipe.	Were appropriate methods used? Yes	**1**
Test conditions	After an equilibration period of 25 hours, samples were collected at several intervals.10 samples collected between 0–119 hours post-equilibration.	Were the test conditions appropriate? Yes, no atmospheric exposure occurred – beneficial when testing a highly volatile substance	**1**
Methods and Observations			
Analytical or other methods described	7 measurements were averaged for the final solubility value. Blanks were used. Blank and standard check performed daily.	Was the test substance analytically verified in the test system using appropriate methods? Yes	**1**
Results			
Findings described	Water solubility of D4 in seawater is 33 ± 3.6 µg/L	Were the findings consistent with the methodology? Yes	**1**
		Score (6–24) :	**6**

Short citation (Author, year, or ID)	**DOWCO07E**		
Full citation (or link)	**Dow Corning Corporation. 2007. Determination of the 1-0ctanol/Water Partition Coefficient of Octamethylcyclotetrasiloxane (D4) by the Slow-Stirring Method Using Gas Chromatography and Mass Spectrometry. HES Study Number: 10198-102.**		
Study type (e.g., OECD Guideline if applicable)	**OECD Guidelines for the Testing of Chemicals, Proposal for a New Guideline, *Partition Co-efficient (1-Octanol/Water): Slow-Stirring Method* (draft, submitted November 2003)**		
Study Director (if applicable)	**Kozerski, G.**		
GLP compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	Octamethylcyclotetrasiloxane (D4); supplied as Dow Corning ® 244 Fluid	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	99.77 ± 0.002 area percent purity	Was the source and purity identified? Yes	**1**
Test Design			
Test system	slow-stirring method as described in OECD 123 guideline. Aqueous phase D4 concentrations are determined by GC-MS using a pre-concentration technique that extracts the test substance from a water sample into a small solvent droplet, which is directly analyzed by GC-MS. Determinations of the much greater D4 concentrations in the octanol phase are made by GC after diluting the sample in a suitable solvent. Three independent determinations of log Kow are made using triplicate test vessels having the same nominal concentration of D4 in the octanol phase.	Were appropriate methods used? Yes	**1**
Test conditions	headspace micro-extraction (HSME) used to extract and concentrate the D4 into a micro-droplet of solvent for direct injection into the GC. Tested in triplicate and tested over 2 days with 5 sampling time points at 24, 30, 49, 54, and 73 hours (performed in duplicate). 6.489 was calculated as the variance weighted average of the individual results as specified in the draft test guideline. Test temperature conditions ranged between 24.8 – 26 °C.	Were the test conditions appropriate? Yes	**1**
Methods and Observations			
Analytical or other methods described	GC-MS used for aqueous phase analysis. GC with FID used for 1-octanol phase analysis.	Was the test substance analytically verified in the test system using appropriate methods? Yes, appropriate for volatile substance.	**1**
Results			
Findings described	Using the slow-stirring method, specifically recommended for measuring values oflog Kow	Were the findings consistent with the methodology?	**1**

Short citation (Author, year, or ID)	**DOWCO07E**		
Full citation (or link)	**Dow Corning Corporation. 2007. Determination of the 1-0ctanol/Water Partition Coefficient of Octamethylcyclotetrasiloxane (D4) by the Slow-Stirring Method Using Gas Chromatography and Mass Spectrometry. HES Study Number: 10198-102.**		
Study type (e.g., OECD Guideline if applicable)	**OECD Guidelines for the Testing of Chemicals, Proposal for a New Guideline, *Partition Co-efficient (1-Octanol/Water): Slow-Stirring Method* (draft, submitted November 2003)**		
Study Director (if applicable)	**Kozerski, G.**		
GLP compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	greater than 4, a log Kow value of 6.488 ± 0.017 (1 SD, n=3) was determined for D4 at 25.1 0 C. This statistically rigorous determination, performed using analytical methods that were shown to be fit-for-purpose, was based on measurements over several days on independent test vessels at a single loading of test substance.		
		Score (6-24):	**6**
Additional notes: published OECD guideline found here: https://www.oecd-ilibrary.org/environment/test-no-123-partition-coefficient-1-octanol-water-slow-stirring-method_9789264015845-en			

Short citation (Author, year, or ID)	**DOWCO07F**		
Full citation (or link)	**Dow Corning Corporation. 2007. Simultaneous determination of partition coefficients for octamethylcyclotetrasiloxane and decamethylcyclopentasiloxane. Report No.: 2007-I0000-58104. Study Number: 10336-101.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study Director (if applicable)	**Xu, S. and B. Kropscott (authors)**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	^{14}C-Octamethyl-cyclotetrasiloxane	Was the test substance identified definitively? Yes, though not clear on how radiolabeled D4 was made.	**1**
Composition (purity, origin); single substance (not mixture)	radiochemical purity was 98.1 %; specific activity 393 mCi/g;	Was the source and purity identified? Yes, though no specifics on radiolabeling.	**1**
Test Design			
Test system	A custom-made glass apparatus which allowed for the establishment of octanol/air/water three-phase equilibrium and for simultaneous determination of K_{AW}, K_{OA} and K_{OW}. A syringe method developed in this work was used to collect samples.	Were appropriate methods used? Yes	**1**
Test conditions	Sampled at various times from 1 up to 94 hours. Equilibrium achieved in laboratory fume hood at 22 °C	Were the test conditions appropriate? Yes	**1**
Methods and Observations			
Analytical or other methods described	^{14}C-labelled D4 and D5 were used as test articles to eliminate background interference. Two step extraction method used for water analysis, a cryogenic gas trap for air analysis. Octanol phase diluted prior to analysis by, HPLC with a radiometric detector, and liquid scintillation counting analysis for radioactivity quantification (two different extraction methods) were used for determining the concentration of D4 in each of the 3 phases.	Was the test substance analytically verified in the test system using appropriate methods? Yes	**1**
Results			
Findings described	Log K_{OW} for D4 is 6.98; log K_{AW} for D4 is 2.69; log K_{OA} for D4 is 4.29 at 21.7°C	Were the findings consistent with the methodology? Yes	**1**
		Score (6–24):	**6**

Short citation (Author, year, or ID)	**DOWCO06A**		
Full citation (or link)	**Dow Corning Corporation. 2006. 1-octanol/air partitioning coefficients of octamethylcyclotetrasiloxane (D4), decamethylcyclopentasiloxane (D5), and dodecamethylcyclohexasiloxane (D6) at different temperatures. HES Study No.: 10163–108.**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**Xu, S.**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	Octamethylcyclotetrasiloxane	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	99.2% purity, provided by Dow	Was the source and purity identified? Yes	**1**
Test Design			
Test system	Octanol and air contained in gas-tight syringe with a valve. ^{14}C-D4 dissolved into octanol and distribution determined between the two phases by using an HPLC equipped with a radiomatic detector. Air samples analyzed by liquid scintillation analyzer.	Were appropriate methods used? Yes	**1**
Test conditions	Temperature controlled environments; two concentrations of D4 used 5 ppb and 1,000 ppm at our temperatures: -5, 7, 23, and 40 °C.	Were the test conditions appropriate? Yes	**1**
Methods and Observations			
Analytical or other methods described	Use of background correction and corrections for counting efficiency used. Identification of outliers.	Was the test substance analytically verified in the test system using appropriate methods? Yes	**1**
Results			
Findings described	Log Koa 4.22 at 24 °C	Were the findings consistent with the methodology? Yes	**1**
		Score (6–24):	**6**

Short citation (Author, year, or ID)	**XU12A**		
Full citation (or link)	**Xu, S., and B. Kropscott. 2012. Method for simultaneous determination of partition coefficients for cyclic volatile methylsiloxanes and dimethylsilanediol. partition properties. Anal. Chem. 84: 1948-1955.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	14-C D4 (other volatile methylsiloxanes also investigated	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	Source: Dow Corning. Specific activity: 393 mCi/g, radiochemical purity 98.1%	Was the source and purity identified? Yes	**1**
Test Design			
Test system	A novel 3-phase equilibrium method was developed. Test compound is introduced to a double-syringe apparatus for equilibration in water, 1-octanol and air phases simultaneously. K_{AW}, K_{OA}, and K_{OW} are obtained from measured concentrations of the test compound in the 3 phases with the same quantitation method.	Were appropriate methods used? Yes	**1**
Test conditions	Temperature at 22 and 25 °C.	Were the test conditions appropriate? Yes	**1**
Methods and Observations			
Analytical or other methods described	Liquid/liquid extraction of water samples followed by concentration and analysis. Air samples collected in cold trap. Octanol samples injected directly. Analysis by reverse phase HPLC/RAM; liquid scintillation counting for total radioactivity. Average recovery 85.1%	Was the test substance analytically verified in the test system using appropriate methods? Yes	**1**
Results			
Findings described	At average temperature of 21.7 ºC, log K_{AW} = 2.69, log K_{OA} = 4.29; log K_{OW} = 6.98	Were the findings consistent with the methodology? Yes	**1**
		Score (6–24):	**6**

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Hydrolysis reviews

Short citation (Author, year, or ID)	**DOWCO04A**		
Full citation (or link)	**Dow Corning Corporation. 2004. Non-regulated study: method development and preliminary assessment of the hydrolysis kinetics of octamethylcyclotetrasiloxane (D4) according to the principles of OECD guideline 111.**		
Study type (e.g., OECD Guideline if applicable)	**OECD Guideline 111(Hydrolysis as a function of pH)**		
Study Director (if applicable)	**Durham, J. and G. Kozerski**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	^{14}C-Octamethylcyclotetrasiloxane	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	Provided by Dow Corning, purity was considered N/A for this study.	Was the source and purity identified? Yes, though purity was not measured.	**2**
Preparation	^{14}C-D4 prepared in tetrahydrofuran (THF) at target concentration of 28 ppb (half the water solubility of D4). Spiking solutions prepared in THF and added using gastight syringe.	Was the test substance preparation described and appropriate for the test system? Yes	**1**
Test Design			
Test system (suitability)	Two-piece reaction experiments (to understand factors affecting degradation rates in different conditions) and sealed tube experiments (recovery/mass balance) ran for 264 hours	Was the test method appropriate for the test substance? Study was investigating appropriate methods that would account for the properties of d4	**1**
Test conditions (monitored and appropriate)	Two-piece vessel experiments in deionized water, octanol saturated water, and pH buffered water. Sealed tube experiments in buffers (pH of 5, 7 and 9). All experiments conducted at 25 °C.	Were test conditions appropriate? Yes	**1**
Consistency (across groups)	The same experimental preparation/set up was used consistently.	Were test conditions consistent across groups? Yes	**1**
Test organisms (if applicable)	N/A	Was the inoculum or test organism appropriate? N/A	**--**
Controls	N/A	Were the appropriate controls used?	**--**
Duration	Up to 264 hours	Was the duration of the study appropriate? Yes	**1**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Half-life, total recovery, and parent D4 percentage	Were the appropriate outcomes reported? Yes	**1**
Control performance	N/A	Was control performance acceptable?	**--**
Sampling adequacy (frequency, duration)	Two-piece vessels sampled at varying time points dependent on the experiment. Common time points	Was the timing and frequency of sampling adequate? Yes	**1**

Short citation (Author, year, or ID)	**DOWCO04A**		
Full citation (or link)	**Dow Corning Corporation. 2004. Non-regulated study: method development and preliminary assessment of the hydrolysis kinetics of octamethylcyclotetrasiloxane (D4) according to the principles of OECD guideline 111.**		
Study type (e.g., OECD Guideline if applicable)	**OECD Guideline 111(Hydrolysis as a function of pH)**		
Study Director (if applicable)	**Durham, J. and G. Kozerski**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	included 0, 2, 4, 8, 24, 48, 96, 168, and 264 hours. No time points were given for the sealed tube experiments.		
Analytical method and measurements of test substance to verify presence in test system	Samples analyzed with liquid scintillation analysis and radio-HPLC. Spiked samples used. Validation of HPLC column recovery performed	Were appropriate methods of analysis used? Yes	**1**
Results			
Confounding variables	Had to conduct mass balance to confirm is loss was due to hydrolysis or volatilization. Used flasks that could be sealed – initial experiment used a two-piece vessel. A number of additional experiments performed to understand effects of vial type and medium (glass v. Teflon, buffered water v. deionized water).	What sources of variability were noted and did they affect the outcome assessment? Yes, variability was noted, and updates made to experimental design to correct for variability.	**1**
Outcomes unrelated to exposure	Systematic decreasing recoveries in experiments made quantification of hydrolysis difficult.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**2**
Data	Half-life of 3.5 days at pH 7 and 25 °C in the two-piece vessels though decreasing recoveries occurred. Sealed tube experiments had half-life of 91 hours at pH 7 and 33 hours at pH 9 (25 °C). n-octanol-water partition coefficient: log kow value of 6.98 at 21.7°C.	Were the data appropriately reported to document the outcome(s)? Yes	**1**
Statistical method and kinetic calculations	Total recovery calculated, percent parent D4 calculated.	Were statistics and/or kinetic calculations described and consistent? Yes	**1**
Plausibility of results	Study factored into the experimental design many of the challenges associated with testing a volatile compound. Precautions were taken to account for variability and additional factors that could lead to experimental error. Results indicate the sealed tube method is feasible.	Were the study results reasonable? Yes	**1**
		Score (14-56):	**17**

Short citation (Author, year, or ID)	**DOWCO05A**		
Full citation (or link)	**Dow Corning Corporation. 2005. Hydrolysis of octamethylcyclotetrasiloxane (D4). Study No.: 10000-102.**		
Study type (e.g., OECD Guideline if applicable)	**OECD Guideline for Testing of Chemicals 111 (Hydrolysis as a function of pH)**		
Study Director (if applicable)	**Durham, J.**		
GLP Compliance (if applicable)	**Yes**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	^{14}C-Octamethylcyclotetrasiloxane	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	98.0 ± 0.21 % purity, provided by Dow Corning	Was the source and purity identified? Yes	**1**
Preparation	Primary stock solution prepared in tetrahydrofuran (THF) as were spiking solutions, to give an initial concentration of 20 ppb nominal, and <1% by volume of THF in the buffered reaction medium	Was the test substance preparation described and appropriate for the test system? Yes, preparation of test solutions and all buffers provided in detail.	**1**
Test Design			
Test system (suitability)	Hydrolysis reactions conducted in thin-walled borosilicate glass tubes in the dark. Temperature controlled by water bath or incubator. Test substance added using gastight syringe. Headspace purged.	Was the test method appropriate for the test substance? Yes	**1**
Test conditions (monitored and appropriate)	Varying temperature (10, 25, and 35 °C) and pH (4, 7, and 9) in flame-sealed borosilicate glass tubes which were sacrificed with each analysis.	Were test conditions appropriate? Yes	**1**
Consistency (across groups)	All experiments performed in same test system	Were test conditions consistent across groups? Yes	**1**
Test organisms (if applicable)	N/A	Was the inoculum or test organism appropriate? N/A	--
Controls	N/A	Were the appropriate controls used?	**--**
Duration	Dependent on experiment, hydrolysis reactions performed up to 500 hours.	Was the duration of the study appropriate? Yes	**1**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Parent compound recovery (mass balance), formation of degradation products, rate constants	Were the appropriate outcomes reported? Yes	**1**
Control performance	Spiked sample used.	Was control performance acceptable?	**--**
Sampling adequacy (frequency, duration)	Dependent on experiment, between 8 – 13 samples collected in over experiment duration	Was the timing and frequency of sampling adequate? Yes	**1**
Analytical method and measurements of test substance to verify presence in test system	Radio-HPLC and liquid scintillation analysis.	Were appropriate methods of analysis used? Yes	**1**

Short citation (Author, year, or ID)	**DOWCO05A**		
Full citation (or link)	**Dow Corning Corporation. 2005. Hydrolysis of octamethylcyclotetrasiloxane (D4). Study No.: 10000-102.**		
Study type (e.g., OECD Guideline if applicable)	**OECD Guideline for Testing of Chemicals 111 (Hydrolysis as a function of pH)**		
Study Director (if applicable)	**Durham, J.**		
GLP Compliance (if applicable)	**Yes**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Results			
Confounding variables	Recovery of 90-110% was not attained, although the experiment was designed for the properties of D4	What sources of variability were noted and did they affect the outcome assessment? Addressed in study report, limited impact	**2**
Outcomes unrelated to exposure	none	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**--**
Data	Average solution recovery of ^{14}C activity was slightly above 80% for reactions conducted at pH 4 and 9, while for pH 7 the average recovery was approximately 70%. Half-life values ranged from 12 minutes at pH 9, 35 °C, to 23 days for pH 7 at 10 °C. The average half-life for pH 7 at 25 °C was 80 hours (3.3 days), in good agreement with previously reported preliminary results. For pH 7.0 at 12 °C, a relevant condition risk assessment purposes for fresh water, the predicted value of the half life is16. 7 days. For pH 8.0 at 9 °C, a condition that is relevant for marine water, the predicted half life is 2.9 days.	Were the data appropriately reported to document the outcome(s)? Yes.	**1**
Statistical method and kinetic calculations	Non-linear regression analysis, estimated rate constants for hydrolysis reaction intermediates, proposed degradation mechanism.	Were statistics and/or kinetic calculations described and consistent? Yes	**1**
Plausibility of results	Considerations made to account for volatility of compound; results are plausible.	Were the study results reasonable? Yes	**1**
		Score (14-56):	**15**

Phototransformation reviews

Short citation (Author, year, or ID)	**BERNA18A**		
Full citation (or link)	**Bernard F, Papanastasiou DK, Papadimitriou VC, Burkholder JB. Temperature Dependent Rate Coefficients for the Gas-Phase Reaction of the OH Radical with Linear (L2, L3) and Cyclic (D3, D4) Permethylsiloxanes. J. Phys Chem 2018, 122, 4252-4264.**		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	Purity 98.0%	Was the source and purity identified?	**2**
Preparation	All samples were degassed in several freeze (77 K)-pump-thaw cycles and stored under vacuum in Pyrex reservoirs. The permethylsiloxanes were introduced into the vacuum system by passing a flow of He carrier gas through a reservoir containing the pure sample. The sample reservoirs were kept at room temperature. The approximate vapor pressure at 294 K is ~0.8 Torr	Was the test substance preparation described and appropriate for the test system?	**--**
Test Design			
Test system (suitability)	Measured pseudo first-order rate constants for reaction with OH radicals using $CF_3CF{=}CH_2$, Z-$CF_3CF{=}CHF$, $CF_2{=}CH_2$, $CH_3CH_2CH_3$ as reference substances in gas-phase reaction chamber (100 cm long Pyrex reactor) with online sampling (infrared absorption+FTIR and UV absorption). OH radicals generated using H2O2, HNO3, or (CH3)COOH + 248 nm pulsed laser UV light.	Was the test method appropriate for the test substance?	**2**
Test conditions (monitored and appropriate)	Temperature range: 270 – 370 K OH radical concentration range: 7.7 - 10.5 *10^{10} mol/cm3 D4 concentration range: 0.19-2.65*10^{15} mol/cm3	Were test conditions appropriate?	**2**
Consistency (across groups)	NA	Were test conditions consistent across groups?	**--**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**--**
Controls	No degradation observed under dark or background conditions	Were the appropriate controls used?	**2**
Duration	No information	Was the duration of the study appropriate?	**3**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Rate constants measured. Thermodynamic and kinetic behaviors calculated.	Were the appropriate outcomes reported?	**2**

Short citation (Author, year, or ID)	**BERNA18A**		
Full citation (or link)	**Bernard F, Papanastasiou DK, Papadimitriou VC, Burkholder JB. Temperature Dependent Rate Coefficients for the Gas-Phase Reaction of the OH Radical with Linear (L2, L3) and Cyclic (D3, D4) Permethylsiloxanes. J. Phys Chem 2018, 122, 4252-4264.**		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Control performance	Blank runs were used. Reference standard behavior not discussed.	Was control performance acceptable?	**2**
Sampling adequacy (frequency, duration)	Experiments repeated at least twice at each temperature. Results within 3% of replicate runs. Sampling frequency and duration are not described.	Was the timing and frequency of sampling adequate?	**2**
Analytical method and measurements of test substance to verify presence in test system	Infrared absorption+FTIR and UV absorption within 7% of each other. Overall analytical uncertainty of 8% and overall uncertainty of 14%. Some verification of chemical purity by GC-MS.	Were appropriate methods of analysis used?	**2**
Results			
Confounding variables	No information	What sources of variability were noted and did they affect the outcome assessment?	**2**
Outcomes unrelated to exposure	NA	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**2**
Data	Rate constant for OH radical at 295 K: $1.12\pm0.01 * 10^{-12}$ $cm^3/mol/s$ Atmospheric half- life approx. 13 days assuming global average OH concentration of 10^6 mol/cm^3.	Were the data appropriately reported to document the outcome(s)? Well-described findings	**1**
Statistical method and kinetic calculations	Rates calculated using reference standard rates. Linear least square fit to calculate rates for replicate runs.	Were statistics and/or kinetic calculations described and consistent?	**1**
Plausibility of results	Very plausible. Results are consistent with other studies by Sommerlade and Atkinson and similar to those by Xiao and Safron. The authors conducted this study to reduce the uncertainty in the rates to use for modeling purposes. The overall uncertainty in the rate is 13% compared to 30-40% for the other authors.	Were the study results reasonable?	**1**
		Range of possible scores: 15-60	**27**

Short citation (Author, year, or ID)	**KIM17A and KIM17B (Supplemental information)**		
Full citation (or link)	**Kim J and S Xu. 2017. Quantitative structure-reactivity relationships of hydroxyl radical rate constants for linear and cyclic volatile methylsiloxanes. Env Tox & Chem. 36 (12) 3240-3245.**		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	D4 Purity >99% from Dow Chemical n-hexane as reference standard from Sigma Aldrich	Was the source and purity identified?	**2**
Preparation	No information	Was the test substance preparation described and appropriate for the test system?	**--**
Test Design			
Test system (suitability)	134 L stainless steel round chamber with two quartz windows. Inside coated with SilcoNert ® 2000. OH radicals generated by ozone from ozone generator and sunlight from solar simulator.	Was the test method appropriate for the test substance?	**2**
Test conditions (monitored and appropriate)	Experiments conducted at 25C and 45% RH. D4 concentration range: 0.29-1.17 ppmV. Ozone and hexane concentrations also varied	Were test conditions appropriate?	**2**
Consistency (across groups)	NA	Were test conditions consistent across groups?	**--**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**--**
Controls	Blank controls used	Were the appropriate controls used?	**2**
Duration	No information	Was the duration of the study appropriate?	**3**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Rate constants measured. Authors also estimate a substitution factor for the methyl groups based OH radical reaction constants.	Were the appropriate outcomes reported?	**2**
Control performance	Blank runs were used. Reference standard behavior not discussed. One experiment repeated 5 times; rates vary by ~ 50%.	Was control performance acceptable?	**2**
Sampling adequacy (frequency, duration)	No information	Was the timing and frequency of sampling adequate?	**3**
Analytical method and measurements of test substance to verify presence in test system	GC-MS used to measure D4 and n-hexane continuously; actual data not presented.	Were appropriate methods of analysis used?	**2**
Results			

Short citation (Author, year, or ID)	KIM17A and KIM17B (Supplemental information)		
Full citation (or link)	Kim J and S Xu. 2017. Quantitative structure-reactivity relationships of hydroxyl radical rate constants for linear and cyclic volatile methylsiloxanes. Env Tox & Chem. 36 (12) 3240-3245.		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Confounding variables	No information	What sources of variability were noted and did they affect the outcome assessment?	--
Outcomes unrelated to exposure	NA	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	--
Data	Rate constant for OH radical at 298 K: 0.95±0.18 *10^{-12} cm^3/mol/s Atmospheric half- life approx. 11.5 days assuming global average OH concentration of 1.5*10^6 mol/cm^3. (Figure S4)	Were the data appropriately reported to document the outcome(s)? Details in SI.	**1**
Statistical method and kinetic calculations	Outlier tests; Grubb's test and Dixon Q test determined that no outliers were present.	Were statistics and/or kinetic calculations described and consistent?	**2**
Plausibility of results	Results are most similar to Atkinson and Bernard, although still similar to Xiao, Sommerlade and Safron. Authors use a slightly different OH radical concentration to estimate the half-life.	Were the study results reasonable?	**1**
		Range of possible scores: 15-60	**25**

Short citation (Author, year, or ID)	XIAO15A		
Full citation (or link)	**Xiao R, Zammit I, Wei Z, Hu WP, McLeod M, Spinney R. 2015. Kinetics and mechanism of the oxidation of cyclic methylsiloxanes by hydroxyl radical in the gas phase: an experimental and theoretical study. Envir. Sci Technol. 49(22): October 2015**		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	Source: Fluka, Purity 99.0%	Was the source and purity identified?	**1**
Preparation	NA	Was the test substance preparation described and appropriate for the test system?	**-**
Test Design			
Test system (suitability)	Measured second-order rate constants for reaction with OH radicals using trimethylpentane as reference substance in gas-phase reaction chamber with online samping (GC/MS). In addition, used theoretical approach (density functional theory).	Was the test method appropriate for the test substance?	**2**
Test conditions (monitored and appropriate)	Chamber housed in GC oven, allowing measurements at 6 different temperatures	Were test conditions appropriate?	**2**
Consistency (across groups)	NA	Were test conditions consistent across groups?	**-**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**-**
Controls	Degradation due to oxidation by ozone, oxygen, or direct photolysis excluded by blank runs. TMP used as reference compound.	Were the appropriate controls used?	**2**
Duration	Cites methodology of Safron et al. 2015	Was the duration of the study appropriate?	**2**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Rate constants measured. Thermodynamic and kinetic behaviors calculated.	Were the appropriate outcomes reported?	**2**
Control performance	Blank runs were used.	Was control performance acceptable?	**2**
Sampling adequacy (frequency, duration)	Measured at 40 and 70°C in duplicate, at 50°C in triplicate, at 90°C in quadruplicate, at 60°C six times, and at 80°C seven times.	Was the timing and frequency of sampling adequate?	**1**
Analytical method and measurements of test substance to verify presence in test system	MS operated in electron ionization mode with selected positive-ion monitoring. After signal plateau was reached, the UV lamp was turned on to initiate OH production. The UV lamp was turned off after the decay of signals was no longer observed	Were appropriate methods of analysis used?	**2**
Results			

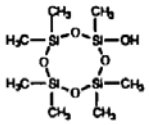
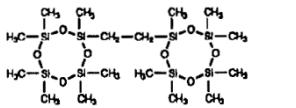
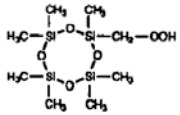
Short citation (Author, year, or ID)	XIAO15A		
Full citation (or link)	Xiao R, Zammit I, Wei Z, Hu WP, McLeod M, Spinney R. 2015. Kinetics and mechanism of the oxidation of cyclic methylsiloxanes by hydroxyl radical in the gas phase: an experimental and theoretical study. Envir. Sci Technol. 49(22): October 2015		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Confounding variables	No information	What sources of variability were noted and did they affect the outcome assessment?	**2**
Outcomes unrelated to exposure	No information	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**2**
Data	Rate constant for OH radical at 298 K: 2.34 x 10^{-12} $cm^3molecule^{-1}s^{-1}$. Arrhenius activation energy: -0.17 kcal/mol with little influence of temperature. Atmospheric half- life approx. 4.5 days assuming global average OH concentration of 7.7 x 10^5 molecules/cm^3	Were the data appropriately reported to document the outcome(s)?	**2**
Statistical method and kinetic calculations	Conventional transition-state theory	Were statistics and/or kinetic calculations described and consistent?	**2**
Plausibility of results	Authors concluded results were reasonably similar to Atkinson 1991 (2x-3x times different). Measured k values were approximately an order of magnitude higher than theoretical.	Were the study results reasonable?	**2**
		Range of possible scores: 15-60	**27**

Short citation (Author, year, or ID)	**SAFRO15A**		
Full citation (or link)	**Safron A. Strandell M, Kierkegaard A., Macleod M. Rate Constants and activation energies for gas-phase reactions of three cyclic volatile methyl siloxanes with the hydroxyl radical. 2015. Journal of Chemical Kinetics pp. 420-428.**		
Study type (e.g., OECD Guideline if applicable)	**Phototransformation**		
Study director (if applicable)			
GLP compliance (Y/N)	N		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, D6 mixture	Was the test substance identified definitively?	**2**
Composition (purity, origin); single substance (not mixture)	Mix of D4, D5, and D6, with cyclohexane (as a kinetic reference standard) and chloromethane. D4 was 99% pure	Was the source and purity identified? Yes but a mixture was used. Impact of use of mixture unclear.	**2**
Preparation	Preparation of chemical mixture described for "typical experiment" as a solution containing mole fractions of 3.3% D4, 2.3% D 5, 2.0% D 6, 20.6% cyclohexane, and 71.8% dichloromethane	Was the test substance preparation described and appropriate for the test system? [This item has not been scored for other phototransformation studies so is left unscored here for consistency]	**--**
Test Design			
Test system (suitability)	Rate constants for reactions with OH radicals were determined by relative rate techniques compared to reference compounds (cyclohexane). Apparatus similar to that used by Hites in other published phototransformation studies. Sealed container, one-time introduction of chemicals and ozone. Turned on UV light to produce OH radicals after stabilization period.	Was the test method appropriate for the test substance?	**2**
Test conditions (monitored and appropriate)	OH radicals generated by presence of O3 with UV light. Measured O3 levels and found to be similar to Hites from his published studies. Estimated OH radical concentration. Monitoring D4, D5, D6, and cyclohexane throughout experiment.	Were test conditions appropriate?	**2**
Consistency (across groups)	See Observations	Were test conditions consistent across groups?	**--**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**--**
Controls	Used reference reagent (cyclohexane). Did not measure phototransformation kinetics for cyclohexane, but assumed a rate of $1.2x10^{-12}$ cm3/mol*s (note this value is different from that cited in Atkinson). Also did not control for hydrolysis since water vapor was present in the chamber. However, in the absence of OH radicals, the D4 levels remain constant indicating negligible hydrolysis.	Were the appropriate controls used? It is likely that there is an error in the paper where the rate for cyclohexane is discussed. If this rate were actually used, the D4 rate coefficient would be approximately 7 times faster and no longer in agreement with other sources.	**2**
Duration	~ 30 minutes	Was the duration of the study appropriate?	**2**

Short citation (Author, year, or ID)	**SAFRO15A**		
Full citation (or link)	**Safron A. Strandell M, Kierkegaard A., Macleod M. Rate Constants and activation energies for gas-phase reactions of three cyclic volatile methyl siloxanes with the hydroxyl radical. 2015. Journal of Chemical Kinetics pp. 420-428.**		
Study type (e.g., OECD Guideline if applicable)	**Phototransformation**		
Study director (if applicable)			
GLP compliance (Y/N)	N		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Test conducted 35 times at 5 different temperatures. Replicate results are reasonably tight. Rates for D4 vary by 30% (at T = 313 K): range from 1.79 E-12 to 2.42 E-12. Rates calculated using two separate equations are also very similar. D4 Phototransformation rate at 298K: 1.9 x 10^{-12} cm3/molecules*sec D4 Phototransformation rate at global troposphere temperature of 255K: 1.45 x 10^{-12} cm3/molecules*sec Assuming global OH radical concentration of 10^{6} molecules/cm3, half-life in troposphere is 8 days.	Were the appropriate outcomes reported?	**2**
Control performance	No description of cyclohexane performance	Was control performance acceptable?	**3**
Sampling adequacy (frequency, duration)	Constant sampling, duration appears long enough to clearly see decay	Was the timing and frequency of sampling adequate?	**2**
Analytical method and measurements of test substance to verify presence in test system	GC-MS	Were appropriate methods of analysis used?	**2**
Results			
Confounding variables	None	What sources of variability were noted and did they affect the outcome assessment?	**2**
Outcomes unrelated to exposure	The OH concentration used in the test is 3 orders of magnitude higher than global concentrations. This may have an impact, although the rate is 2^{nd} order to account for the OH concentration	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**2**
Data	Data present in supporting information. However, no data on cyclohexane	Were the data appropriately reported to document the outcome(s)?	**1**
Statistical method and kinetic calculations	Regression analysis conducted. P values are << 0.05	Were statistics and/or kinetic calculations described and consistent?	**1**
Plausibility of results	Results are similar (2 x faster) to those published by Atkinson	Were the study results reasonable?	**2**

Short citation (Author, year, or ID)	**SAFRO15A**		
Full citation (or link)	**Safron A. Strandell M, Kierkegaard A., Macleod M. Rate Constants and activation energies for gas-phase reactions of three cyclic volatile methyl siloxanes with the hydroxyl radical. 2015. Journal of Chemical Kinetics pp. 420-428.**		
Study type (e.g., OECD Guideline if applicable)	**Phototransformation**		
Study director (if applicable)			
GLP compliance (Y/N)	N		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
		Score (15-60):	**29**

Short citation (Author, year, or ID)	SOMMER93A		
Full citation (or link)	**Sommerlade, R., et al. 1993. Product Analysis and Kinetics of the Gas-Phase Reactions of Selected Organosilicon Compounds with OH radicals using a smog chamber-mass spectrometer system. Environ. Sci. Technol. 27, 2435-2440.**		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	octamethylcyclotetrasiloxane	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	Source: Bayer AG. Purity not specified	Was the source and purity identified?	**1**
Preparation	NA	Was the test substance preparation described and appropriate for the test system?	**--**
Test Design			
Test system (suitability)	Rate constant for OH radical reaction determined with smog chamber coupled with quadrupole mass spectrometer, by comparison to relative rates for reference compound (n-hexane). Irradiation with a mercury high pressure lamp at maximum light intensity with irradiation times of 2 – 300 min.	Was the test method appropriate for the test substance?	**2**
Test conditions (monitored and appropriate)	297 ± 2 K, 70 Torr total pressure of gas, $2.8*10^{15}$ mol/cm3 D4 concentration in the chamber	Were test conditions appropriate?	**2**
Consistency (across groups)	NA	Were test conditions consistent across groups?	**--**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**--**
Controls	No information	Were the appropriate controls used?	**3**
Duration	2 – 300 min.	Was the duration of the study appropriate?	**2**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Concentrations over time measured by on-line mass spectrometer and used to calculate rate constant using n-hexane as a reference compound	Were the appropriate outcomes reported?	**2**
Control performance	Errors 2 times least squares standard deviations	Was control performance acceptable?	**2**
Sampling adequacy (frequency, duration)	Concentrations of parent compounds and reference substance determined continuously.	Was the timing and frequency of sampling adequate?	**2**
Analytical method and measurements of test substance to verify presence in test system	Structures of reaction products identified by GC-MS and GC-FTIR	Were appropriate methods of analysis used?	**2**
Results			
Confounding variables	No information	What sources of variability were noted and did they affect the outcome assessment?	**2**

Short citation (Author, year, or ID)	SOMMER93A		
Full citation (or link)	**Sommerlade, R., et al. 1993. Product Analysis and Kinetics of the Gas-Phase Reactions of Selected Organosilicon Compounds with OH radicals using a smog chamber-mass spectrometer system. Environ. Sci. Technol. 27, 2435-2440.**		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Outcomes unrelated to exposure	None reported	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**2**
Data	Rate constant for OH radical reaction: 1.26 x 10^{-12} $cm^3molecule^{-1}s^{-1}$. A variety of different conversion products were formed, including the following major products: heptamethylhydroxycyclotetrasiloxane  1,2-bis(heptamethylcyclotetrasiloxanyl)ethane  heptamethyl(hydroperoxymethyl)cyclotetrasiloxane 	Were the data appropriately reported to document the outcome(s)?	**2**
Statistical method and kinetic calculations	Rate constants determined by relative rates of decay of test compound compared to organic reference compound.	Were statistics and/or kinetic calculations described and consistent?	**2**
Plausibility of results	Rate constant ($1.26*10^{-12}$) is similar to that measured by Atkinson ($1.01*10^{-12}$) and Safron ($1.9*10^{-12}$).	Were the study results reasonable?	**2**
		Range of possible scores: 15-60	**29**

Short citation (Author, year, or ID)	ATKIN91A		
Full citation (or link)	Atkinson R. 1991. Kinetics of the gas-phase reactions of a series of organosilicon compounds with OH and NO3 radicals and D3. Environ Sci Technol. 25(5):863–866		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	octamethylcyclotetrasiloxane	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	98% purity, from Aldrich Chemical Co.. No impurities detected by GC-FID.	Was the source and purity identified?	**1**
Preparation	NA	Was the test substance preparation described and appropriate for the test system?	**--**
Test Design			
Test system (suitability)	Rate constants for reactions with OH and NO3 radicals were determined by relative rate techniques compared to reference compounds (cyclohexane for OH radical reactions and n-heptane for NO3 radical reactions). Upper limits of rate constants determined by monitoring decay in the presence of O3.	Was the test method appropriate for the test substance?	**2**
Test conditions (monitored and appropriate)	Irradiated at maximum light intensity for 2-20 min. Carried out in 6400-L all Teflon chamber equipped with 2 banks of black lamps. Carried out at 297 ± 2 K and ca. 740 Torr total pressure of air. Monitored by GC-FID.	Were test conditions appropriate?	**2**
Consistency (across groups)	No information	Were test conditions consistent across groups?	**--**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**--**
Controls	No information	Were the appropriate controls used?	**3**
Duration	2- 20 minutes	Was the duration of the study appropriate?	**2**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Concentrations over time measured by GC-FID and used to calculate rate constants	Were the appropriate outcomes reported?	**2**
Control performance	No information	Was control performance acceptable?	**2**
Sampling adequacy (frequency, duration)	No information	Was the timing and frequency of sampling adequate?	**3**
Analytical method and measurements of test substance to verify presence in test system	GC-FID, 10 ft x 0.125 in. SS column of 10% Carbowax E-600 on C-22 firebrick, operated at 373 K. Replicate analyses yielded precision ≤ 3%	Were appropriate methods of analysis used?	**2**
Results			
Confounding variables	Avoided formation of O3 and NO3 by generating OH radicals by photolysis in air of methyl nitrite	What sources of variability were noted and did they affect the outcome assessment?	**2**

Short citation (Author, year, or ID)	ATKIN91A		
Full citation (or link)	Atkinson R. 1991. Kinetics of the gas-phase reactions of a series of organosilicon compounds with OH and NO3 radicals and D3. Environ Sci Technol. 25(5):863–866		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Outcomes unrelated to exposure	No information	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**2**
Data	Photolysis not significant during experiment. Little reaction with NO3 or O3. Rate constants in cm^3 $molecule^{-1}$ s^{-1}: for OH radical: 1.01 x 10^{-12}; for O3 radical: <2x10^{-18}; for O3 reactions: <3x10^{-20}. Note that although the O3 reaction rates were so slow they were hard to quantify, since O3 concentrations are orders of magnitude greater than OH radical concentrations, applying these O3 rate constants to the O3 concentration could result in a meaningful half-life.	Were the data appropriately reported to document the outcome(s)?	**2**
Statistical method and kinetic calculations	Concentrations over time used to determine rate constants, as related to reference organic	Were statistics and/or kinetic calculations described and consistent?	**2**
Plausibility of results	Results reasonable and consistent with Sommerlade and Safron.	Were the study results reasonable?	**2**
		Range of possible scores:15-60	**30**

Short citation (Author, year, or ID)	**BAYER90A**		
Full citation (or link)	**Photochemical Degradability of octamethylcyclotetrasiloxane in gaseous phase. Bayer report, June 25, 1990**		
Study type (e.g., OECD Guideline if applicable)			
Study Director (if applicable)	**Parlar, H.**		
GLP compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	octamethylcyclotetrasiloxane	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	Not reported	Was the source and purity identified?	**3**
Preparation	NA	Was the test substance preparation described and appropriate for the test system?	**--**
Test Design			
Test system (suitability)	Spherical reactor vessel with varying volume 4-20 liters. Xenon lamp at 290 nm. Analysis by GC-MS.	Was the test method appropriate for the test substance?	**2**
Test conditions (monitored and appropriate)	Humidity of 40%. D4 concentrations of 1, 5, and 10 ppm. D4 reacted with nitrogen, oxygen, and air in the presence and absence of water. 10 ppm D4 also reacted with OH radicals. OH radical concentration not specified.	Were test conditions appropriate? OH radical concentration not reported.	**3**
Consistency (across groups)	NA	Were test conditions consistent across groups?	**--**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**--**
Controls	Used n-octane, toluene, benzene, and ethylbenzene as reference chemicals	Were the appropriate controls used?	**2**
Duration	24 hours	Was the duration of the study appropriate?	**2**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	D4 was stable in the presence of nitrogen, oxygen, air and water for 24 hours. D4 decayed in the presence of OH radicals with radical rate constant measured as $3.08*10^{-12}$ cm3/s at 27°C. [Note that units do not include $molecule^{-1}$.] Degradation products similar to those determined by Sommerlade.	Were the appropriate outcomes reported?	**2**
Control performance	Reported oh reaction rate constants of reference chemicals	Was control performance acceptable?	**2**
Sampling adequacy (frequency, duration)	No information	Was the timing and frequency of sampling adequate?	**3**
Analytical method and measurements of test substance to verify presence in test system	GC-MS	Were appropriate methods of analysis used?	**2**

Short citation (Author, year, or ID)	**BAYER90A**		
Full citation (or link)	**Photochemical Degradability of octamethylcyclotetrasiloxane in gaseous phase. Bayer report, June 25, 1990**		
Study type (e.g., OECD Guideline if applicable)			
Study Director (if applicable)	**Parlar, H.**		
GLP compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Results			
Confounding variables	No information	What sources of variability were noted and did they affect the outcome assessment?	**2**
Outcomes unrelated to exposure	No information	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**2**
Data	Uncertainty when comparing with findings reported elsewhere because units are not simiilar	Were the data appropriately reported to document the outcome(s)?	**3**
Statistical method and kinetic calculations	Not described	Were statistics and/or kinetic calculations described and consistent?	**3**
Plausibility of results	Results are slightly higher than those determined by Atkinson, Safron, Sommerlade, and Xiao, assuming the units are comparable.	Were the study results reasonable?	**2**
		Range of possible scores:15-60	**34**

Short citation (Author, year, or ID)	ABE81A		
Full citation (or link)	Abe Y., Butler GB, Hogen-Esch TE. 1981. Photolytic Oxidative Degradation of octamethylcyclotetrasiloxane and related compounds. J. of Macromol. Sci-Chem. A16(2) pp. 461-471		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D3, tetramethylsilane	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	Not reported	Was the source and purity identified?	**3**
Preparation	NA	Was the test substance preparation described and appropriate for the test system?	**--**
Test Design			
Test system (suitability)	1L Pyrex flask vessel, O3 added to vessel, O2/N2 or O2/He atmosphere. 150W xenon-mercury lamp generating UV light ≥ 290nm.	Was the test method appropriate for the test substance?	**2**
Test conditions (monitored and appropriate)	25C temperature, atmospheric pressure; O3 concentrations of 10^{-3} mol/L; n-octane used as reference chemical	Were test conditions appropriate?	**2**
Consistency (across groups)	No information	Were test conditions consistent across groups?	**--**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**--**
Controls	n-octane used as reference chemical	Were the appropriate controls used?	**2**
Duration	200 minutes	Was the duration of the study appropriate?	**2**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Rates increased with increasing O3 concentrations. Rates decreased when water was added. D4 may transform to compound with hydroxyl groups and ultimately condense to siloxanes and water. Relative half-life (compared to n-octane) with O3 at ~10^{-3} mol/L is 3.3 days. Note that actual atmospheric O3 concentrations are ~ 10^{-9} mol/L. In the presence of oxygen and similar concentrations of ozone, degradation was faster with half-lives of 0.5-2 h.	Were the appropriate outcomes reported?	**2**
Control performance	N-octane rate data presented, but not discussed	Was control performance acceptable?	**3**
Sampling adequacy (frequency, duration)	Samples collected every ~20-30 minutes over 200 minutes.	Was the timing and frequency of sampling adequate?	**2**
Analytical method and measurements of test substance to verify presence in test system	GC-MS. Samples collected periodically by syringe.	Were appropriate methods of analysis used?	**2**
Results			

Short citation (Author, year, or ID)	ABE81A		
Full citation (or link)	Abe Y., Butler GB, Hogen-Esch TE. 1981. Photolytic Oxidative Degradation of octamethylcyclotetrasiloxane and related compounds. J. of Macromol. Sci-Chem. A16(2) pp. 461-471		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Confounding variables	No information	What sources of variability were noted and did they affect the outcome assessment?	**2**
Outcomes unrelated to exposure	No information	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**2**
Data	Relative half-life (compared to n-octane) with O3 at ~10^{-3} mol/L is 3.3 days. Note that actual atmospheric O3 concentrations are ~ 10^{-9} mol/L	Were the data appropriately reported to document the outcome(s)?	**2**
Statistical method and kinetic calculations	Linear regression but no specifics provided	Were statistics and/or kinetic calculations described and consistent?	**3**
Plausibility of results	Rates are reported as relative to n-octane and thus hard to translate. Experiment conducted at high concentrations of ozone relative to atmosphere, so extrapolation to real-world conditions is uncertain.	Were the study results reasonable?	**3**
		Range of possible scores: 15- 60	**33**

Short citation (Author, year, or ID)	**DOWCO80A**		
Full citation (or link)	**Dow Corning Corporation. 1980. Photochemical oxidation of methylsilicon moieties in the gas phase. Dow Corning Report 5187.**		
Study Director (if applicable)	**Lane, T.H.**		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D3, D2	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	"readily available laboratory samples" used "only after distillation and analysis to insure purity" but purity not reported	Was the source and purity identified?	**2**
Preparation	NA	Was the test substance preparation described and appropriate for the test system?	**--**
Test Design			
Test system (suitability)	1L Glass or Teflon-lined gas sampling bulb. Separation by GC and analysis by IR. Selected samples analyzed by GC-MS. Nitrogen dioxide, nitric acid, and nitroethane used to produce radicals. n-hexane used as reference standard	Was the test method appropriate for the test substance?	**2**
Test conditions (monitored and appropriate)	UV light at 290 to 450 nm; ambient temperature; $7.2*10^{-4}$ mol/L D4, $4.4*10^{-4}$ mol/L water. No monitoring of OH radical production. Samples collected periodically via syringe from reaction vessel.	Were test conditions appropriate?	**2**
Consistency (across groups)	NA	Were test conditions consistent across groups?	**--**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**--**
Controls	Yes, multiple for D3: dark conditions, no water, just UV, etc.	Were the appropriate controls used?	**2**
Duration	Not specified	Was the duration of the study appropriate?	**3**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Half-life of D4 of 0.3 -0.5 days in Teflon bulb and 1.1 days in glass bulb. Rate constants not reported.	Were the appropriate outcomes reported?	**2**
Control performance	Reported only for D3	Was control performance acceptable?	**3**
Sampling adequacy (frequency, duration)	Not specified	Was the timing and frequency of sampling adequate?	**3**
Analytical method and measurements of test substance to verify presence in test system	GC-IR and GC-MS	Were appropriate methods of analysis used?	**2**
Results			

Short citation (Author, year, or ID)	**DOWCO80A**		
Full citation (or link)	**Dow Corning Corporation. 1980. Photochemical oxidation of methylsilicon moieties in the gas phase. Dow Corning Report 5187.**		
Study Director (if applicable)	**Lane, T.H.**		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Confounding variables	None reported	What sources of variability were noted and did they affect the outcome assessment?	**2**
Outcomes unrelated to exposure	None	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**2**
Data	Detailed data and graphs not reported	Were the data appropriately reported to document the outcome(s)?	**3**
Statistical method and kinetic calculations	Rate was pseudo first-order. Half-life of D4 of 0.3-0.5 days in Teflon bulb and 1.1 days in glass bulb.	Were statistics and/or kinetic calculations described and consistent?	**2**
Plausibility of results	An order of magnitude faster than other publications, based on reported half-life. Author found rate was pseudo first-order, compared to other publications which have calculated second order rates. Relative reactivity compared to n-octane is 3.3 as reported in Abe 1981.	Were the study results reasonable?	**2**
		Range of possible scores 15-60:	**33**

Short citation (Author, year, or ID)	**NAVEA09B**
Full citation (or link)	**Navea JG, Stanier CO, Young MA, Grassian VH. 2009b. A Laboratory and Modeling Study at the University of Iowa Designed to Better Understand the Atmospheric Fate of D4 and D5. Final Report (August 2006 – July 2007) Centre Européen des Silicones (CES).**
Study type (e.g., OECD Guideline if applicable)	**Both a laboratory investigation and a modeling study are described in this 54-page report. The laboratory study is reviewed in NAVEA09A.**

Discussion: This report describes a laboratory investigation (see Navea et al. 2009a) and a modeling study. The modeling study employs a box model and uses using rates measured by Navea et al. 2009a, Atkinson 1991 and Sommerlade 1993. The box model provided an atmospheric lifetime for D4 of 9.21 days with OH radical concentration of 10^6 molecule/m3. Model accounting for diurnal changes in D4 and OH radical concentrations in July (full sun) estimated a half-life of 7.4 days. When an aerosol surface concentration of $1.1x10^{-3}$ m^2/m^3 is included in the model, the half-life ranges from 7.69 days (20% humidity) to 8.75 days (60% humidity). The box model also simulated concentrations in urban, transition, and rural areas. Tables 5 and 6 of the report include OH concentrations for urban and rural areas.

Remarks: The results of the box model should be considered in the discussion of environmental modeling.

Short citation (Author, year, or ID)	NAVEA09A		
Full citation (or link)	**Navea JG, Xu S, Stanier CO, Young M A, Grassian VH. 2009a. Effect of ozone and relative humidity on the heterogenous uptake of octamethylcyclotetrasiloxane and decamethylcyclopentasiloxane on model mineral dust aerosol components. J. Phys. Chem. A. 113:7030–7038.**		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	Source: Dow Corning. >99.5% purity	Was the source and purity identified?	**1**
Preparation	NA	Was the test substance preparation described and appropriate for the test system?	**--**
Test Design			
Test system (suitability)	Heterogeneous photolysis of gas phase D4 on atmospheric particles in the presence of O3 was studied in an environmental aerosol/photolysis chamber. 0.15 m3 stainless steel cylinder chamber internally coated with Teflon. D4 exposed to kaolinite, hematite, and carbon black (all of >99% purity)	Was the test method appropriate for the test substance?	**2**
Test conditions (monitored and appropriate)	Relative humidity (RH) was monitored to investigate the influence of surface adsorbed water on the heterogeneous chemistry of mineral dust (kaolinite, hematite) and carbon black samples. Concentrations monitored continuously with FT-IR. 725 ppm D4 initial concentration.	Were test conditions appropriate? Initial concentration of D4 was very high	**3**
Consistency (across groups)	NA	Were test conditions consistent across groups?	**--**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**--**
Controls	Reference experiments conducted with single component mixtures (e.g O3 only) at various RH	Were the appropriate controls used?	**2**
Duration	400 minutes based on figures presented	Was the duration of the study appropriate?	**2**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Uptake kinetics and reaction extent	Were the appropriate outcomes reported?	**2**
Control performance	Reference experiments showed negligible loss to walls	Was control performance acceptable?	**2**
Sampling adequacy (frequency, duration)	Sampling frequency illustrated in figures	Was the timing and frequency of sampling adequate?	**2**
Analytical method and measurements of test substance to verify presence in test system	Time-dependent loss of D4 and O3 monitored using FT-IR spectrophotometer	Were appropriate methods of analysis used?	**2**

Short citation (Author, year, or ID)	NAVEA09A		
Full citation (or link)	**Navea JG, Xu S, Stanier CO, Young M A, Grassian VH. 2009a. Effect of ozone and relative humidity on the heterogenous uptake of octamethylcyclotetrasiloxane and decamethylcyclopentasiloxane on model mineral dust aerosol components. J. Phys. Chem. A. 113:7030–7038.**		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Results			
Confounding variables	None noted	What sources of variability were noted and did they affect the outcome assessment?	**2**
Outcomes unrelated to exposure	None noted	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**2**
Data	Elevated RH increased total uptake of D4 and O3 by the end of the experiment. The atmospheric loss of D4 due to heterogeneous uptake is enhanced due to O3 but the overall loss rate is reduced at RH values typical of the troposphere. Authors believe that D4 is polymerizing on the particulate matter surface in the presence of O3. The polymerization rate is not measured. Uptake rate onto the particulate matter surface for D4 at 40% relative humidity is $1.8*10^{10}$ /cm2*s (cm2 is surface area of particulate matter).	Were the data appropriately reported to document the outcome(s)?	**2**
Statistical method and kinetic calculations	Fit of experimental data (decay over time)	Were statistics and/or kinetic calculations described and consistent?	**2**
Plausibility of results	Results suggest that atmospheric oxidants such as O3 may modify the mineral dust surface such that uptake of D4 by mineral dust may be important. Tests were conducted only up to 60% relative humidity, therefore rates at higher humidities are unknown	Were the study results reasonable? Conducted at O3 concentration 3-4 orders of magnitude greater than those at sea level. Highly pure mineral and carbon black samples would have provided maximum surface sorption area. However, findings indicate potential for uptake on these components of aerosols and the effect of RH and O3.	**2**
		Range of possible scores: 15-60	**29**

Short citation (Author, year, or ID)	KIM16A		
Full citation (or link)	Kim J and Xu S. 2016. Sorption and desorption kinetics and isotherms of volatile methylsiloxanes with atmospheric aerosols. Chemosphere 144:555-563		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	Source: Dow Corning. >99.5% purity	Was the source and purity identified?	**1**
Preparation	NA	Was the test substance preparation described and appropriate for the test system?	**--**
Test Design			
Test system (suitability)	Sorption and desorption of D4 onto 9 different aerosol types was studied in an environmental aerosol chamber. GC-FID used for D4 analysis. Aerosols were kaolinite, illite, mica, hematite, quartz, carbon black, sea salt, ammonium sulfate, and ammonium hydrogen sulfate.	Was the test method appropriate for the test substance?	**2**
Test conditions (monitored and appropriate)	Teflon bag equilibrated to 30% relative humidity and room temperature (21C). Materials ground to aerosol sized particles and dried at 120C in an oven. Aerosol (11-464 ug/m3) added concurrently with D4 (91-389 ug/L) in a syringe to the test chamber. Samples removed via syringe at specific timepoints to measure concentrations. Desorption tested by removing half of the air from the test chamber (without aerosols) and replacing with clean air at 30% RH.	Were test conditions appropriate?	**2**
Consistency (across groups)	NA	Were test conditions consistent across groups?	**--**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**--**
Controls	Control with no aerosols tested to determine sorption to test chamber walls.	Were the appropriate controls used?	**2**
Duration	48 hours	Was the duration of the study appropriate?	**2**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Sorption and desorption kinetics and sorption isotherms. Specific rates and coefficients depend on specific aerosol. Aerosol-air partition coefficient range from 0.09 to 50.4 L/m2 for D4.	Were the appropriate outcomes reported? Results are well-described.	**1**
Control performance	5.3%-7% of D4 sorbed to walls. Negligible desorption.	Was control performance acceptable?	**1**

Short citation (Author, year, or ID)	KIM16A		
Full citation (or link)	**Kim J and Xu S. 2016. Sorption and desorption kinetics and isotherms of volatile methylsiloxanes with atmospheric aerosols. Chemosphere 144:555-563**		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Sampling adequacy (frequency, duration)	Samples collected at 1 min, 12 mins, 30 mins, 2 hrs, 24 hrs and 48 hrs. Sorption had already occurred by 1 minute.	Was the timing and frequency of sampling adequate?	**2**
Analytical method and measurements of test substance to verify presence in test system	D4 concentrations measured using GC-FID	Were appropriate methods of analysis used?	**2**
Results			
Confounding variables	No information	What sources of variability were noted and did they affect the outcome assessment?	**2**
Outcomes unrelated to exposure	No information	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**2**
Data	For most aerosols, D4 fully absorbed within 2 hours and most within the first minute. Sorption isotherms were best fit to Freundlich and Polanyi-Manes, except for carbon black with best fit to a Langmuir isotherm. Carbon black and kaolinite showed the largest sorption density; sea salt was the lowest. Sorption onto carbon black, sea salt, and quartz was reversible. Sorption onto kaolinite and sulfate was irreversible indicating some type of irreversible interaction between D4 and the aerosol.	Were the data appropriately reported to document the outcome(s)?	**2**
Statistical method and kinetic calculations	Fit of experimental data to different isotherm types using goodness of fit models.	Were statistics and/or kinetic calculations described and consistent?	**2**
Plausibility of results	Results indicate that D4 readily sorbs to aerosols. The D4 and aerosol concentrations used are ~10^6 times higher than environmentally relevant levels, but the authors argue that the cVMS concentrations on aerosols could be similar to that in the real environment.	Were the study results reasonable? Relative humidity plays an important role in sorption (see Navea 2009A). These tests were carried out at 30% relative humidity, which is the approximately the daytime humidity in the desert, and thus not environmentally relevant for most atmospheric conditions.	**2**
		Range of possible scores: 15-60	**26**

Short citation (Author, year, or ID)	NAVEA09C		
Full citation (or link)	**Navea JG, Xu S, Stanier CO, Young MA, Grassian VH. 2009c. Heterogeneous uptake of octamethylcyclotetrasiloxane (D4) and decamethylcyclopentaasiloxane (D5) onto mineral dust aerocsol under variable RH conditions. Atmospheric Environment. 43 4060-4069.**		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	No information	Was the source and purity identified?	**3**
Preparation	NA	Was the test substance preparation described and appropriate for the test system?	**--**
Test Design			
Test system (suitability)	Investigated heterogeneous uptake of D4 onto different types of particulate matter (hematite, kaolinite, quartz, calcite, and carbon black, al >99% purity). Uptake of gaseous D4 measured onto particulate matter using an environmental aerosol reaction chamber (0.15 m3 stainless steel chamber internally coated with Teflon)	Was the test method appropriate for the test substance?	**2**
Test conditions (monitored and appropriate)	Relative humidity (RH) monitored. Initial concentrations of D4 were 725 ppm and 230 ppm. FT-IR used to monitor concentrations continuously	Were test conditions appropriate?	**2**
Consistency (across groups)	NA	Were test conditions consistent across groups?	**--**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**--**
Controls	No information	Were the appropriate controls used?	**3**
Duration	400 minutes based on figures presente4d	Was the duration of the study appropriate?	**2**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Measured uptake over time. Best sorption was onto clay particles. Significant drop in sorption rates with increasing relative humidity. Does not consider transformation on the surfaces of the particulate matter	Were the appropriate outcomes reported?	**2**
Control performance	NA	Was control performance acceptable?	**2**
Sampling adequacy (frequency, duration)	Sampling frequency illustrated in figures	Was the timing and frequency of sampling adequate?	**2**
Analytical method and measurements of test substance to verify presence in test system	Time-dependent loss of D4 and O3 monitored using FT-IR spectrophotometer.	Were appropriate methods of analysis used?	**2**
Results			

Short citation (Author, year, or ID)	NAVEA09C		
Full citation (or link)	**Navea JG, Xu S, Stanier CO, Young MA, Grassian VH. 2009c. Heterogeneous uptake of octamethylcyclotetrasiloxane (D4) and decamethylcyclopentaasiloxane (D5) onto mineral dust aerocsol under variable RH conditions. Atmospheric Environment. 43 4060-4069.**		
Study type (e.g., OECD Guideline if applicable)			
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Confounding variables	No information	What sources of variability were noted and did they affect the outcome assessment?	**2**
Outcomes unrelated to exposure	No information	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**2**
Data	Data presented primarily as figures. Data show D4 can be removed from the gas phase by reaction with components of mineral dust aerosol and carbon black under dry, ≤ 1% RH conditions. However uptake decreased with increasing RH.	Were the data appropriately reported to document the outcome(s)?	**2**
Statistical method and kinetic calculations	Calculated rate constants by measuring decay over time	Were statistics and/or kinetic calculations described and consistent?	**2**
Plausibility of results	Results suggest that partitioning to aerosol surfaces may be in important loss pathway for D4. However, sorption rates are significantly lower at typical ambient relative humidities.	Were the study results reasonable? Highly pure mineral and carbon black samples would have provided maximum surface sorption area. Results at ≤1% RH are not realistic for most environments. However, findings indicate potential for uptake on these components of aerosols.	**2**
		Range of possible scores: 15-60	**31**

Short citation (Author, year, or ID)	XU19A		
Full citation (or link)	**Xu, S., Warner, N., Bohlin-Nizzetto, P., Durham, J. and McNett, D., 2019. Long-range transport potential and atmospheric persistence of cyclic volatile methylsiloxanes based on global measurements. Chemosphere, 228: 460–468.**		
Study type (e.g., OECD Guideline if applicable)	NA		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, and D6	Was the test substance identified definitively? No. Data was mined from previously published reports and literature. No summary table was provided on the forms of D4, D5, and D6.	**2**
Composition (purity, origin); single substance (not mixture)	Information not provided.	Was the source and purity identified? No. D4, D5, and D6 data were mined from literature and government reports. No summary was provided on the composition of D4, D5, and D6 from the various reports and literature.	**2**
Preparation	NA	Was the test substance preparation described and appropriate for the test system?	**--**
Test Design			
Test system (suitability)	Air monitoring data was mined from peer-reviewed journals and government reports for analysis.	Was the test method appropriate for the test substance? Yes.	**1**
Test conditions (monitored and appropriate)	700 measurements of outdoor air concentrations were taken from peer-reviewed journals and government reports between 2004 and 2016 with the latitudes of the sampling sites ≥35ºN. Air monitoring data from immediate point sources such as manufacture sites, waste water treatment plants and landfills were excluded to avoid bias. Data from locations south of 35ºN latitude in Europe and North America were used for spatial pattern analysis. Data from Asian locations were not included due to scarcity for establishing trends at the corresponding geography as well as the minimal influence Asian air masses will have on the tested Europe transect based on the global air circulation patterns.	Were test conditions appropriate? Yes, samples were collected from an appropriate latitude from previously published reports and literature. A large dataset (~700 measurements) and eliminating known sources with inflated data (point sources such as manufacturing sites) likely reduced any data biases.	**1**
Consistency (across groups)	For all data, regardless of sampling/analytical methodology, a data screening evaluation was performed. The interspecies correlation between different cVMS compounds measured at the same times and locations were used to check if any given subset of data fell in the 95% prediction intervals of the entire dataset. This data cleaning procedure is based on the assumption that D4, D5 and D6 have the same sources and similar removal mechanisms. Special point sources or sample contamination will result in data falling outside the	Were test conditions consistent across groups? Data clean up and statistical analyses were developed to create consistency across all of the data.	**1**

Short citation (Author, year, or ID)	XU19A		
Full citation (or link)	**Xu, S., Warner, N., Bohlin-Nizzetto, P., Durham, J. and McNett, D., 2019. Long-range transport potential and atmospheric persistence of cyclic volatile methylsiloxanes based on global measurements. Chemosphere, 228: 460–468.**		
Study type (e.g., OECD Guideline if applicable)	NA		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	intervals and these data were thus considered as outliers and excluded from the spatial pattern analysis.		
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	--
Controls	NA	Were the appropriate controls used?	--
Duration	NA	Was the duration of the study appropriate?	--
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Data from locations south of 35ºN latitude in Europe and North America were used for spatial pattern analysis.	Were the appropriate outcomes reported? Yes, data from northern latitudes were the appropriate observation for understanding atmospheric fate.	**1**
Control performance	NA	Was control performance acceptable?	--
Sampling adequacy (frequency, duration)	700 measurements used, taken from 2004 to 2016	Was the timing and frequency of sampling adequate? Yes.	**2**
Analytical method and measurements of test substance to verify presence in test system	No analytical measurements were used – data was measured by other studies and analyzed in this study. The study used spatial patterns analysis for D4, D5, and D6.	Were appropriate methods of analysis used? Yes.	**2**
Results			
Confounding variables	Yes, a data screening step was conducted to eliminate data that came from point sources that may result in outliers, and a data imputation method was used to reduce sample biases. It was expected that the model predictions (i.e. average concentrations in the modeled spatial scale), could not predict the concentration spikes present in cities even with exclusion of point sources in these regions as the models lack the required spatial resolution. The match between predicted and measured contaminant concentrations in the global environment is subject to many variables, with accurate emission data being an essential input. In this context, emission data includes emission rate, mode and spatial patterns. However, accurate emission data are not available for North America and Asia, although the total emission rates of all three cVMS were estimated for European Continent.	What sources of variability were noted, and did they affect the outcome assessment?	**2**

Short citation (Author, year, or ID)	XU19A		
Full citation (or link)	**Xu, S., Warner, N., Bohlin-Nizzetto, P., Durham, J. and McNett, D., 2019. Long-range transport potential and atmospheric persistence of cyclic volatile methylsiloxanes based on global measurements. Chemosphere, 228: 460–468.**		
Study type (e.g., OECD Guideline if applicable)	NA		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	The study also discusses artifacts related to sampling and analytical methods, the quality of data for D4, and assumptions used in calculations.		
Outcomes unrelated to exposure	NA	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**--**
Data	South-north spatial concentration gradients were examined with respect to the sample location latitude for all data passing the simple screening. Three major trends were observed. First, D4 and D6 concentrations were correlated with measured concentrations for D5 at the same times and locations in the majority of the datasets, reflecting the common sources and similar removal mechanism(s) for these compounds. Second, as the sampling sites changed from the source to remote locations along a south to north transect, average cVMS concentrations in air decreased in an exponential manner. The empirical characteristic travel distances (eCTD) extracted from these spatial patterns were smaller than model estimated values and differed in order among individual compounds (D4 ~ D5 < D6). Finally, D5/D6 concentration ratios were also found to decrease exponentially along the same spatial gradient, contrary to model predictions of an increase based on current knowledge of mechanisms controlling atmospheric cVMS degradation. These findings suggest that there may be additional removal process(es) for airborne cVMS, currently not accounted for, that requires further elucidation.	Were the data appropriately reported to document the outcome(s)? Yes.	**1**
Statistical method and kinetic calculations	Measurements below method detection limits (MDL) were given a value of half of the corresponding MDL from the same studies for statistical analysis. Published values between MDL and limit of quantitation (LOQ) were used without change. For measurements recorded as "< LOQ", the average values of LOQ and MDL were assumed for measurements if no specific value was accessible. This data imputation method was implemented to reduce the	Were statistics and/or kinetic calculations described and consistent? Yes.	**2**

Short citation (Author, year, or ID)	XU19A		
Full citation (or link)	**Xu, S., Warner, N., Bohlin-Nizzetto, P., Durham, J. and McNett, D., 2019. Long-range transport potential and atmospheric persistence of cyclic volatile methylsiloxanes based on global measurements. Chemosphere, 228: 460–468.**		
Study type (e.g., OECD Guideline if applicable)	NA		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	bias in calculating the average concentrations and found not to affect the interspecies correlation mentioned above.		
Plausibility of results	The real-life degradation of D4, D5 and D6 in air may be much faster than what is currently estimated. The authors have demonstrated that D4, D5 and D6 may be transported much shorter distances in the real atmosphere than estimated using models based on the OH radical mechanism. In addition, the data suggest that the spatial patterns of the D4, D5 and D6 concentration ratios cannot be explained by OH radical mechanism alone, suggesting that additional degradation mechanism(s) are operative in the atmosphere for these compounds. This work suggests that the real-life half-life may be much shorter (~2 days) than the experimentally determined half-life.	Were the study results reasonable? Yes.	**1**
		Range of possible scores:12-48	**18**

Biodegradation reviews

Short citation (Author, year, or ID)	SPRIN05B		
Full citation (or link)	Springborn Smithers Laboratories. 2005b. Determining the biodegradability of octamethylcyclotetrasiloxane based on the draft OECD 310 sealed vessel CO_2 evolution biodegradation test. Study No.: 12023.6146.		
Study type (e.g., OECD Guideline if applicable)	OECD 310 Sealed Vessel CO_2 Evolution Biodegradation Test (a screening method for the evaluation of ready biodegradability)		
Study director (if applicable)	Gledhill, W.E.		
GLP Compliance (Y/N)	Y		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	99.7% purity. Source: Aldrich	Was the source and purity identified?	**1**
Preparation	3.5 µL added to 107 mL of mineral medium to give 10 mg C/L	Was the test substance preparation described and appropriate for the test system? Yes this is below the reported water solubility of 0.056 mg/L	**1**
Test Design			
Test system (suitability)	Consisted of 160 mL glass serum bottles containing 107 mL medium and sealed with Teflon-lined caps. 27 bottles for test substance, 27 for toxicity control, 27 for reference substance, and 27 for inoculum control.	Was the test method appropriate for the test substance? Yes, this method permits testing of water soluble and insoluble plus volatile materials	**1**
Test conditions (monitored and appropriate)	In the dark, temperature ranged from 20.8 to 21.6°C. Mixed continuously on rotary shaker table	Were test conditions appropriate?	**1**
Consistency (across groups)	Test vessels placed in incubator and sampled randomly	Were test conditions consistent across groups?	**1**
Test organisms (if applicable)	Activated sludge from domestic WWTP. Centrifuged supernatant washed and diluted with mineral medium to give 10 mg solids/L. Also, 10 mg of soil filtrate added to each L of activate sludge inoculum.	Was the inoculum or test organism appropriate?	**1**
Controls	Inoculated medium controls, sodium benzoate reference substance controls, toxicity controls (D4 and reference substance)	Were the appropriate controls used? Yes, however blank controls were not included	**2**
Duration	29 days	Was the duration of the study appropriate?	**1**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	TIC measured and used to calculate % biodegradation (net cumulative % CO_2 evolved)	Were the appropriate outcomes reported?	**1**

Short citation (Author, year, or ID)	**SPRIN05B**		
Full citation (or link)	**Springborn Smithers Laboratories. 2005b. Determining the biodegradability of octamethylcyclotetrasiloxane based on the draft OECD 310 sealed vessel CO_2 evolution biodegradation test. Study No.: 12023.6146.**		
Study type (e.g., OECD Guideline if applicable)	**OECD 310 Sealed Vessel CO_2 Evolution Biodegradation Test (a screening method for the evaluation of ready biodegradability)**		
Study director (if applicable)	**Gledhill, W.E.**		
GLP Compliance (Y/N)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Control performance	Reference substance biodegradation peaked at 104% and was >60% within a 10-day window of reaching 10% CO_2 production, confirming viable microbial population.	Was control performance acceptable?	**1**
Sampling adequacy (frequency, duration)	Triplicate vessels removed on days 2,4,7,10, 14, 21 and 29	Was the timing and frequency of sampling adequate? Yes, although guideline requires 5 replicates analyzed at test termination to enable calculation of 95% confidence interval.	**2**
Analytical method and measurements of test substance to verify presence in test system	At each sampling interval, phosphoric acid injected to terminate biological activity and release CO_2 gas. Vessels shaken for ≥ 60 min. 1.0 mL of headspace gas analyzed for TIC (total inorganic carbon) on TOC analyzer and used to calculate total amount of CO_2 evolved	Were appropriate methods of analysis used?	**1**
Results			
Confounding variables	None noted	What sources of variability were noted and did they affect the outcome assessment?	**1**
Outcomes unrelated to exposure	None noted. Random treatment of test vessels.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**1**
Data	Mean biodegradation of D4 peaked at 16.2% of theoretical at day 21 and was 3.70% of theoretical at day 29, indicating little biodegradation. No toxicity was indicated (54.6% biodegradation i the toxicity control).	Were the data appropriately reported to document the outcome(s)? Replicate values, means and SD provided. Graphical display of CO_2 evolution over time	**1**
Statistical method and kinetic calculations	Percent degradation calculated relative to starting TOC. No statistical analysis	Were statistics and/or kinetic calculations described and consistent? Did not sample 5 replicates at end so 95% confidence limits could not be reported	**2**
Plausibility of results	Results reasonable	Were the study results reasonable?	**1**
		Score (18-72):	**21**

Short citation (Author, year, or ID)	**SPRIN91D**		
Full citation (or link)	**Springborn Laboratories, Inc. 1991d. (Octamethylcycotetrasiloxane) – determination of the biodegradability in a sediment/soil microbial system. SLI Report #91-01-3640. 12 Feb 1991.**		
Study type (e.g., OECD Guideline if applicable)	**Bourquin microcosm (EPA-600/3-75-035), modified to address D4 properties**		
Study director (if applicable)	**Fackler, P.**		
GLP compliance (Y/N)	**Y with minor exceptions**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	^{14}C-D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	Source: Wizard Laboratories, Davis CA. Specific activity 28.4 mCi/mmole, 99% purity	Was the source and purity identified?	**1**
Preparation	Primary stock solution prepared in acetone, diluted and used to fortify test systems (3 µg D4 added to 90 mL water and 15 mL sediment)	Was the test substance preparation described and appropriate for the test system?	**1**
Test Design			
Test system (suitability)	Glass core chambers fitted with inlet and outlet ports from which air passed through a Tenax trap connected to a scintillation vial containing KOH to trap evolved $^{14}CO_2$. Sediment layer 3 cm deep, water layer 10 cm deep, air layer 1 cm deep.	Was the test method appropriate for the test substance? Design was modified to address D4 volatility, but still resulted in some backflow.	**2**
Test conditions (monitored and appropriate)	Sediment (3.2 % organic carbon, pH 5.5) and water from Horseshoe Pond, Wareham MA. Environmental chamber at 25±2°C. After 72-h equilibration, aerated for 10 minutes every 72 hours.	Were test conditions appropriate?	**1**
Consistency (across groups)	Controls and sterile controls treated the same.	Were test conditions consistent across groups?	**1**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**--**
Controls	2 sterile controls for days 14, 28, 42 and 56	Were the appropriate controls used?	**1**
Duration	56 days	Was the duration of the study appropriate?	**1**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Radioactivity in each compartment determined at each sampling time and expressed as percent of total radioactivity initially applied. Also, number of colony forming units per g sediment determined for each vessel.	Were the appropriate outcomes reported?	**1**
Control performance	Sterile controls showed no microbial growth	Was control performance acceptable?	**1**
Sampling adequacy (frequency, duration)	2 replicates for each sampling interval (0, 7, 14, 21, 28, 35, 42, and 56 days).	Was the timing and frequency of sampling adequate?	**1**

Short citation (Author, year, or ID)	**SPRIN91D**		
Full citation (or link)	**Springborn Laboratories, Inc. 1991d. (Octamethylcycotetrasiloxane) – determination of the biodegradability in a sediment/soil microbial system. SLI Report #91-01-3640. 12 Feb 1991.**		
Study type (e.g., OECD Guideline if applicable)	**Bourquin microcosm (EPA-600/3-75-035), modified to address D4 properties**		
Study director (if applicable)	**Fackler, P.**		
GLP compliance (Y/N)	**Y with minor exceptions**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Analytical method and measurements of test substance to verify presence in test system	At each sampling interval, Tenax traps removed, eluted with methanol and assayed for radioactivity by LSC and HPLC/RAM. Duplicate aliquots from CO_2 traps analyzed by LSC. Water and sediment (after combustion) analyzed by LSC (non-extractable) and HPLC-RAM (extractable). Mean recovery for QC samples was 73.6% ± 14.0%for water and 72.3% ±17.6% for sediment.	Were appropriate methods of analysis used?	**2**
Results			
Confounding variables	"Degradation" occurred in both the active and sterile control chambers, indicating that biodegradation was not necessarily responsible. Backflow into the traps was apparent. Mass balance was variable and often ranged below 80%. Amount of ^{14}C measured in sediment was very variable in replicates for the same time point.	What sources of variability were noted and did they affect the outcome assessment?	**3**
Outcomes unrelated to exposure	High variability among replicates.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**3**
Data	All active chambers had viable microbial populations, while sterile controls did not. Biodegradation was not observed and losses were likely due to hydrolysis or adsorbed compound from backflow.	Were the data appropriately reported to document the outcome(s)? Data tables provided. Variability unable to be addressed since only 2 replicates.	**3**
Statistical method and kinetic calculations	No statistical analyses	Were statistics and/or kinetic calculations described and consistent?	**3**
Plausibility of results	Reasons for results were explained, however the high variability weakens the conclusions	Were the study results reasonable?	**3**
		Score (17-68):	**29**

Short citation (Author, year, or ID)	**DOWCO08C**		
Full citation (or link)	**Dow Corning Corporation. 2008. Aerobic transformation of octamethylcyclotetrasiloxane (D4) in water/sediment systems. Study No.: 10714-108.** **Note: this is an interim report of preliminary results.**		
Study type (e.g., OECD Guideline if applicable)	**OECD 308 (aerobic and anaerobic transformation in aquatic sediment systems) with modifications**		
Study director (if applicable)	**Xu, S and J.A. Miller (authors)**		
GLP compliance (Y/N)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	^{14}C-D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	No information	Was the source and purity identified?	**2**
Preparation	Spiking solution prepared in di(ethylene glycol) methyl ether. Applied via syringe to multiple points in the surface layer of sediment	Was the test substance preparation described and appropriate for the test system?	**1**
Test Design			
Test system (suitability)	Custom made incubation vessel with minimized head space. Direct spiking of D4 into sediment instead of water.	Was the test method appropriate for the test substance? Recovery of total radioactivity averaged 96.7% after 22 days, indicating suitability of test system	**1**
Test conditions (monitored and appropriate)	Sediment (sandy silt) and water collected from Sanford Lake, MI. 2.95% organic carbon, pH of overlying water 6.91-6.99. Sediment:water ratio 4:1. Acclimated 7-12 days prior to D4 addition. Room temperature (22-25 °C) and darkness. Twice daily aeration during acclimation. Aeration 2x/day starting the 3rd day after test substance addition, for 7 days, then every other day.	Were test conditions appropriate? This was a preliminary study so conditions were not tightly controlled	**2**
Consistency (across groups)	No information	Were test conditions consistent across groups?	**3**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**-**
Controls	No information	Were the appropriate controls used?	**2**
Duration	22 days	Was the duration of the study appropriate?	**2**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Measurements of headspace, water and sediment	Were the appropriate outcomes reported?	**2**
Control performance	No information	Was control performance acceptable?	**2**
Sampling adequacy (frequency, duration)	Sampled at 0.08, 6, 11, 14,8, 19.8 and 21.8 days,	Was the timing and frequency of sampling adequate?	**2**

Short citation (Author, year, or ID)	**DOWCO08C**		
Full citation (or link)	**Dow Corning Corporation. 2008. Aerobic transformation of octamethylcyclotetrasiloxane (D4) in water/sediment systems. Study No.: 10714-108.** **Note: this is an interim report of preliminary results.**		
Study type (e.g., OECD Guideline if applicable)	**OECD 308 (aerobic and anaerobic transformation in aquatic sediment systems) with modifications**		
Study director (if applicable)	**Xu, S and J.A. Miller (authors)**		
GLP compliance (Y/N)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Analytical method and measurements of test substance to verify presence in test system	Trapped CO_2 in headspace analyzed by LSC; water analyzed by HPLC with radioactivity detection; sediment analyzed by extraction and HPLC with radioactivity detection for relative concentration of parent and transformation products and by LSC for total radioactivity.	Were appropriate methods of analysis used?	**2**
Results			
Confounding variables	Preliminary experiment was not able to determine if degradation was biotic or abiotic.	What sources of variability were noted and did they affect the outcome assessment?	**3**
Outcomes unrelated to exposure	No information	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**2**
Data	In the first 22 days, about 32% of the D4 underwent hydrolysis in the sediment. Calculated half-life of 47 days. Complete mineralization of D4 or hydrolysis products to CO_2 was not significant during 3 weeks.	Were the data appropriately reported to document the outcome(s)? Actual results not provided in this preliminary study. Percent distribution in air, water and sediment at each sampling day was tabulated.	**3**
Statistical method and kinetic calculations	No information	Were statistics and/or kinetic calculations described and consistent?	**3**
Plausibility of results	Reasonable for preliminary study	Were the study results reasonable?	**2**
		Score (17-68):	**35**

Short citation (Author, year, or ID)	**DOWCO09A**		
Full citation (or link)	**Dow Corning Corporation. 2009a. Aerobic transformation of octamethylcyclotetrasiloxane (^{14}C-D4) in aquatic sediment systems. HES Study No.: 10885-108.**		
Study type (e.g., OECD Guideline if applicable)	**OECD 308 (aerobic and anaerobic transformation in aquatic sediment systems) with modifications**		
Study Director (if applicable)	**Xu, S.**		
GLP compliance (Y/N)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	^{14}C-D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	Source: Dow Corning. Radiochemical purity 97.0 ± 0.10%. Specific activity: 393.490 ± 2.26 mCi/g	Was the source and purity identified?	**1**
Preparation	Spiking solution prepared in di(ethylene glycol) methyl ether. Applied via syringe to multiple points in the surface layer of sediment	Was the test substance preparation described and appropriate for the test system?	**1**
Test Design			
Test system (suitability)	Custom made incubation vessel with minimized head space. Direct spiking of ^{14}C-D4 into sediment instead of water at an initial sediment concentration of 130 – 270 ng/g (dry weight basis).	Was the test method appropriate for the test substance?	**1**
Test conditions (monitored and appropriate)	Sediment collected from Lake Pepin, WI. 3.7% organic carbon, pH 7.9. Acclimated 1-4 weeks prior to D4 addition. Incubated at 24.0 – 26.4°C and darkness. Twice daily aeration during acclimation. After test substance addition, used air exchange process.	Were test conditions appropriate? Normally two different sediments are used.	**2**
Consistency (across groups)	Each vessel contained 25 g sediment and 40 mL water (weighed).	Were test conditions consistent across groups?	**1**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**-**
Controls	Two control vessels with no test substance. Sterile controls (autoclaved) with D4 added. Sodium azide (chemically sterile) controls with D4 added.	Were the appropriate controls used?	**1**
Duration	156 days (autoclaved controls for 59.8 days and sodium azide controls for 98 days)	Was the duration of the study appropriate?	**1**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Measurements of headspace, water and sediment. Evolved CO_2 collected in traps during air exchange and sacrifice.	Were the appropriate outcomes reported?	**1**
Control performance	Degradation in autoclaved controls was faster and in the sodium azide controls slower than for active samples. May be an artifact in the former; results for the latter may indicate microbial activity has a role	Was control performance acceptable? Results did not definitively elucidate biotic vs abiotic degradation.	**2**

Short citation (Author, year, or ID)	**DOWCO09A**		
Full citation (or link)	**Dow Corning Corporation. 2009a. Aerobic transformation of octamethylcyclotetrasiloxane (^{14}C-D4) in aquatic sediment systems. HES Study No.: 10885-108.**		
Study type (e.g., OECD Guideline if applicable)	**OECD 308 (aerobic and anaerobic transformation in aquatic sediment systems) with modifications**		
Study Director (if applicable)	**Xu, S.**		
GLP compliance (Y/N)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Sampling adequacy (frequency, duration)	Two samples at each time point (vessels sacrificed). Sterile controls sampled 6 times, other vessels (active) sampled 18 times over the experiment.	Was the timing and frequency of sampling adequate?	**1**
Analytical method and measurements of test substance to verify presence in test system	Trapped CO_2 in headspace analyzed by HPLC/RAM and LSC; triplicate water samples analyzed by HPLC/RAM; sediment analyzed by extraction and HPLC/RAM and by LSC. Bound residue in sediment determined by combustion using a Biological Oxidizer. Blanks analyzed.	Were appropriate methods of analysis used?	**1**
Results			
Confounding variables	Recovery lower in active vessels (84.7%) compared to sterile vessels (101%) but likely due to their more frequent aeration.	What sources of variability were noted and did they affect the outcome assessment? Recovery was acceptable in active vessels despite more frequent aeration	**2**
Outcomes unrelated to exposure	None.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**1**
Data	Total mass balance or recovery of radioactivity calculated at each sampling time. Results reported as percentages. Average total recovery for all samples, all media: 90.3% ± 13.1%. After day 0, 98% of the D4 is in the sediment. The low fraction in air suggests partition equilibrium not attained (owing to minimum disturbance). The half-life in sediment was 242 days. A substantial fraction of D4 was converted to silanols indicating hydrolysis occurs. Complete mineralization of D4 or hydrolysis products very slow.	Were the data appropriately reported to document the outcome(s)? Percent distribution in air, water and sediment at each sampling day was tabulated. Results presented graphically.	**1**
Statistical method and kinetic calculations	Pseudo first order kinetics model used to determine half-life. Three pairs of samples with recovery <75% excluded from calculation which was then based on 88.5% recovery.	Were statistics and/or kinetic calculations described and consistent?	**1**
Plausibility of results	Reasonable	Were the study results reasonable?	**1**
		Score (17-68):	**20**

Short citation (Author, year, or ID)	**DOWCO09B**		
Full citation (or link)	**Dow Corning Corporation. 2009b. Anaerobic transformation of octamethylcyclotetrasiloxane (^{14}C-D4) in aquatic sediment systems. HES Study No.: 11101-108.**		
Study type (e.g., OECD Guideline if applicable)	**OECD 308 (aerobic and anaerobic transformation in aquatic sediment systems) with modifications**		
Study Director (if applicable)	**Xu, S.**		
GLP compliance (Y/N)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	^{14}C-D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	Source: Dow Corning. Radiochemical purity 97.0 ± 0.10%. Specific activity: 393.490 ± 2.26 mCi/g	Was the source and purity identified?	**1**
Preparation	Spiking solution prepared in di(ethylene glycol) methyl ether. Applied via syringe to multiple points in the surface layer of sediment	Was the test substance preparation described and appropriate for the test system?	**1**
Test Design			
Test system (suitability)	Custom made incubation vessel with minimized head space. Direct spiking of ^{14}C-D4 into sediment instead of water at an initial sediment concentration of 200 – 270 ng/g (dry weight basis).	Was the test method appropriate for the test substance?	**1**
Test conditions (monitored and appropriate)	Sediment collected from Lake Pepin, WI. 3.7% organic carbon, pH 7.9. Acclimated 1-4 weeks prior to D4 addition. Incubated at 23.1 – 24.4°C and darkness. Gas exchange once per week during acclimation, with nitrogen gas. Subsequent gas exchange with nitrogen gas.	Were test conditions appropriate? Normally two different sediments are used.	**2**
Consistency (across groups)	Each vessel contained 25 g sediment and 40 mL water (weighed).	Were test conditions consistent across groups?	**1**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**-**
Controls	Two control vessels with no test substance. Sodium azide (chemically sterile) controls with D4 added.	Were the appropriate controls used?	**1**
Duration	204 days (sodium azide controls for 153 days)	Was the duration of the study appropriate?	**1**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Measurements of headspace, water and sediment.	Were the appropriate outcomes reported?	**1**
Control performance	Degradation in sodium azide controls was slightly higher than the non-sterilized samples.	Was control performance acceptable? Results suggest that degradation may be abiotic.	**2**

Short citation (Author, year, or ID)	**DOWCO09B**		
Full citation (or link)	**Dow Corning Corporation. 2009b. Anaerobic transformation of octamethylcyclotetrasiloxane (^{14}C-D4) in aquatic sediment systems. HES Study No.: 11101-108.**		
Study type (e.g., OECD Guideline if applicable)	**OECD 308 (aerobic and anaerobic transformation in aquatic sediment systems) with modifications**		
Study Director (if applicable)	**Xu, S.**		
GLP compliance (Y/N)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Sampling adequacy (frequency, duration)	Two samples at each time point (vessels sacrificed). Sterile controls sampled 8 times, other vessels (active) sampled 9 times over the experiment.	Was the timing and frequency of sampling adequate?	**1**
Analytical method and measurements of test substance to verify presence in test system	Headspace analyzed by HPLC/RAM and LSC with methane analyzed by combustion using a Biological Oxidizer followed by LSC. Triplicate water samples analyzed by HPLC/RAM. Sediment analyzed by extraction and HPLC/RAM and by LSC. Bound residue in sediment determined by combustion using a Biological Oxidizer. Blanks analyzed.	Were appropriate methods of analysis used?	**1**
Results			
Confounding variables	Slightly lower recovery in active vessels (97.3%) compared to sterile vessels (105.1%) but likely due to their more frequent gas exchange and longer duration.	What sources of variability were noted and did they affect the outcome assessment?	**2**
Outcomes unrelated to exposure	None.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**1**
Data	Total mass balance or recovery of radioactivity calculated at each sampling time. Results reported as percentages. Average total recovery for all samples, all media: 101.1% ± 13.0%. The fraction of D4 in the sediment is >97% across all samples. The low fraction in air suggests partition equilibrium not attained (owing to minimum disturbance). The half-life in sediment was 365 days. Methanogenesis not significant. A substantial fraction of D4 was converted to silanols indicating hydrolysis occurs. Complete mineralization of D4 or hydrolysis products very slow.	Were the data appropriately reported to document the outcome(s)? Percent distribution in air, water and sediment at each sampling day was tabulated. Results presented graphically.	**1**
Statistical method and kinetic calculations	Pseudo first order kinetics model used to determine half-life. Calculation based on % recovery.	Were statistics and/or kinetic calculations described and consistent?	**1**
Plausibility of results	Reasonable	Were the study results reasonable?	**1**
		Score (17-68):	**20**

Short citation (Author, year, or ID)	**XU99B**		
Full citation (or link)	**Xu S, and G. Chandra. 1999. Fate of cyclic methylsiloxanes in soils. 2. Rates of degradation and volatilization. Environ. Sci. Technol. 33:4034–4039.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study director (if applicable)	**N/A**		
GLP compliance (Y/N)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	^{14}C-D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	Radiolabeled D4 from Wizard Laboratories, Davis CA, >99% purity.	Was the source and purity identified?	**1**
Preparation	Prepared in pentane	Was the test substance preparation described and appropriate for the test system?	**1**
Test Design			
Test system (suitability)	2 soils were used: Londo from Bay County, MI (2.4% organic matter, pH 7.6) and highly weathered Wahiawa soil from Oahu, HI (2.2% organic matter, pH 4.9). 5 g of soil placed in tubes and spiked with D4; some tubes left open and others closed to examine both degradation and volatilization.	Was the test method appropriate for the test substance? System appropriate for investigation goals	**1**
Test conditions (monitored and appropriate)	Room temperature (22±2°C). Relative humidity (RH) at 32, 92 and 100% in closed tubes and 32 and 100% in open tubes.	Were test conditions appropriate? Monitoring of conditions not well described	**2**
Consistency (across groups)	Yes except for manipulated variables	Were test conditions consistent across groups?	**1**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**--**
Controls	NA	Were the appropriate controls used?	**--**
Duration	21 days for closed tubes, 15 days for open tubes	Was the duration of the study appropriate?	**1**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Fraction of D4 remaining over time used to calculate rate constants and half-lives	Were the appropriate outcomes reported?	**1**
Control performance	NA	Was control performance acceptable?	**--**
Sampling adequacy (frequency, duration)	Two tubes of each soil sampled at each time interval (7 time points)	Was the timing and frequency of sampling adequate?	**1**
Analytical method and measurements of test substance to verify presence in test system	Following extraction, samples were combusted using a biological oxidizer. Analysis by LSC and reverse phase HPLC.	Were appropriate methods of analysis used?	**1**
Results			

Short citation (Author, year, or ID)	**XU99B**		
Full citation (or link)	**Xu S, and G. Chandra. 1999. Fate of cyclic methylsiloxanes in soils. 2. Rates of degradation and volatilization. Environ. Sci. Technol. 33:4034–4039.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study director (if applicable)	**N/A**		
GLP compliance (Y/N)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Confounding variables	Sources noted and explained (for example temporary accumulation of large non-extractable intermediates causing large variation at short incubation time)	What sources of variability were noted and did they affect the outcome assessment?	**2**
Outcomes unrelated to exposure	None	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**1**
Data	Degradation rate constants and half-lives were calculated from data for closed tubes. Half lives were 0.04, 0.08 and 0.89 days for Wahiawa soil at RH of 32, 92 and 100%, respectively and 3.54 and 5.25 days for Londo soil at RH of 32 and 92%, respectively. At high humidity, degradation slowed and volatilization became predominant. Both processes act to reduce persistence of D4 in soils	Were the data appropriately reported to document the outcome(s)? Most data presented graphically; table of degradation rate constants and half-lives	**2**
Statistical method and kinetic calculations	Pseudo first order degradation rate constants determined and half-lives calculated.	Were statistics and/or kinetic calculations described and consistent?	**1**
Plausibility of results	Results reasonable	Were the study results reasonable?	**1**
		Score (15-60):	**18**

Short citation (Author, year, or ID)	XU99A		
Full citation (or link)	**Xu S. 1999. Fate of cyclic methylsiloxanes in soils. 1. The degradation pathway. Environmental Science and Technology, 33:603–608.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study director (if applicable)	**N/A**		
GLP compliance (Y/N)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	^{14}C-D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	Radiolabeled D4 from Wizard Laboratories, Davis CA, >99% purity.	Was the source and purity identified?	**1**
Preparation	Prepared in pentane	Was the test substance preparation described and appropriate for the test system?	**1**
Test Design			
Test system (suitability)	Wahiawa soil from Oahu, HI (2.2% organic matter, pH 4.9) was used. 1 or 5 g of soil placed in tubes and spiked with D4 and incubated under closed conditions.	Was the test method appropriate for the test substance? System appropriate for investigation goals	**1**
Test conditions (monitored and appropriate)	Room temperature and darkness.	Were test conditions appropriate? Monitoring of conditions not well described	**2**
Consistency (across groups)	NA	Were test conditions consistent across groups?	**--**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**--**
Controls	NA	Were the appropriate controls used?	**--**
Duration	10 min to 7 days	Was the duration of the study appropriate?	**1**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Degradation products	Were the appropriate outcomes reported?	**1**
Control performance	NA	Was control performance acceptable?	**--**
Sampling adequacy (frequency, duration)	Not described.	Was the timing and frequency of sampling adequate?	**2**
Analytical method and measurements of test substance to verify presence in test system	Following extraction, samples were analyzed by GC/MS, gel permeation chromatography (GPC) and reverse phase HPLC to determine degradation products.	Were appropriate methods of analysis used?	**1**
Results			
Confounding variables	NA	What sources of variability were noted and did they affect the outcome assessment?	**--**

Short citation (Author, year, or ID)	**XU99A**		
Full citation (or link)	**Xu S. 1999. Fate of cyclic methylsiloxanes in soils. 1. The degradation pathway. Environmental Science and Technology, 33:603–608.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study director (if applicable)	**N/A**		
GLP compliance (Y/N)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Outcomes unrelated to exposure	NA	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**--**
Data	Degradation steps include ring-opening hydrolysis to form linear oligomeric siloxane diols, followed by further hydrolysis to form monomer dimethylsilanediol.	Were the data appropriately reported to document the outcome(s)?	**1**
Statistical method and kinetic calculations	NA	Were statistics and/or kinetic calculations described and consistent?	**--**
Plausibility of results	Results reasonable	Were the study results reasonable?	**1**
		Score (11-44):	**13**

Short citation (Author, year, or ID)	**DOWCO07A**		
Full citation (or link)	**Dow Corning Corporation. 2007a. Estimation of degradation rates of cVMS in soils, HES Study No. 10787-102. November 2007.**		
Study type (e.g., OECD Guideline if applicable)	**Data extrapolation to estimate degradation rates in an "average" soil**		
Study director (if applicable)	**Xu, S. (author)**		
GLP compliance (Y/N)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity		Was the test substance identified definitively?	
Composition (purity, origin); single substance (not mixture)		Was the source and purity identified?	
Preparation		Was the test substance preparation described and appropriate for the test system?	
Test Design			
Test system (suitability)	Not a lab study. Based on data from XU99A and XU99B	Was the test method appropriate for the test substance?	
Test conditions (monitored and appropriate)		Were test conditions appropriate?	
Consistency (across groups)		Were test conditions consistent across groups?	
Test organisms (if applicable)		Was the inoculum or test organism appropriate?	
Controls		Were the appropriate controls used?	
Duration		Was the duration of the study appropriate?	
Methods and Observations			
Observations (half-lives, coefficients, etc.)	For a given cVMS in any soil, the hydrolysis rate can be estimated from the relative humidity of the air at equilibrium with the soil.	Were the appropriate outcomes reported?	
Control performance		Was control performance acceptable?	
Sampling adequacy (frequency, duration)		Was the timing and frequency of sampling adequate?	
Analytical method and measurements of test substance to verify presence in test system		Were appropriate methods of analysis used?	
Results			
Confounding variables		What sources of variability were noted and did they affect the outcome assessment?	
Outcomes unrelated to exposure		Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	

Short citation (Author, year, or ID)	**DOWCO07A**		
Full citation (or link)	**Dow Corning Corporation. 2007a. Estimation of degradation rates of cVMS in soils, HES Study No. 10787-102. November 2007.**		
Study type (e.g., OECD Guideline if applicable)	**Data extrapolation to estimate degradation rates in an "average" soil**		
Study director (if applicable)	**Xu, S. (author)**		
GLP compliance (Y/N)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Data	Conclusion: D4 half-life in a temperate soil is 4.1 – 5.27 days (relative humidity 50 – 90%). In a tropical soil this would be 0.046 – 0.078 days (relative humidity 50-90%)	Were the data appropriately reported to document the outcome(s)?	
Statistical method and kinetic calculations		Were statistics and/or kinetic calculations described and consistent?	
Plausibility of results		Were the study results reasonable?	

Soil adsorption and desorption reviews

Short citation (Author, year, or ID)	DOWCO07B		
Full citation (or link)	Dow Corning Corporation. 2007b. Soil-water distribution of octamethycyclotetrasiloxane (D4) using a batch equilibrium method, study No. 10439-108. Nov. 11, 2007.		
Study type (e.g., OECD Guideline if applicable)	OECD 106, Adsorption-desorption using batch equilibrium		
Study director (if applicable)	Miller, J.		
GLP compliance (Y/N)	Y		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	^{13}C-D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	99.8% purity by GC-FID. Source: Dow Corning	Was the source and purity identified?	**1**
Preparation	Prepared in dimethylformamide	Was the test substance preparation described and appropriate for the test system?	**1**
Test Design			
Test system (suitability)	3 soils (slit loam, sandy loam, and sandy clay loam/sandy loam) and 0.01M calcium chloride in deionized water. Soils ranged in organic carbon content from 2.0 – 5.5% and in pH from 5.5- 8.3. ^{13}C-D4 spiked into individual test units rather than the equilibrated soil at initial concentration of 41 ng/mL (below water solubility limit). Isotherms studied at concentrations covering two orders of magnitude	Was the test method appropriate for the test substance? Yes, adjusted for low water solubility of D4. Used direct method, which is more accurate than indirect (mass balance) method. Also, prepared separate vessels for sampling rather than repeated sampling of same vessels, to minimize volatilization.	**1**
Test conditions (monitored and appropriate)	Soil: solution ratio at 1:20 (determined based on preliminary trial). Equilibrated over night with mixing. Temperature 24.8±0.1 °C	Were test conditions appropriate?	**1**
Consistency (across groups)	Groups treated similarly	Were test conditions consistent across groups?	**1**
Test organisms (if applicable)	NA	Was the inoculum or test organism appropriate?	**--**
Controls	Duplicate blanks (no D4).	Were the appropriate controls used? Traditional controls were not used due to the difficulty maintaining stable D4 concentrations in aqueous phase.	**2**
Duration	30 h	Was the duration of the study appropriate?	**1**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Direct measurement of the amount of D4 adsorbed onto soil and the amount in test solution.	Were the appropriate outcomes reported? Used direct method, which is more accurate than indirect (mass balance) method. Also, prepared separate vessels for sampling rather than repeated sampling of same vessels, to minimize volatilization.	**1**

Short citation (Author, year, or ID)	**DOWCO07B**		
Full citation (or link)	**Dow Corning Corporation. 2007b. Soil-water distribution of octamethycyclotetrasiloxane (D4) using a batch equilibrium method, study No. 10439-108. Nov. 11, 2007.**		
Study type (e.g., OECD Guideline if applicable)	**OECD 106, Adsorption-desorption using batch equilibrium**		
Study director (if applicable)	**Miller, J.**		
GLP compliance (Y/N)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Control performance	Blanks did show D4 but values were significantly low that blank correction of results was not necessary.	Was control performance acceptable?	**2**
Sampling adequacy (frequency, duration)	Duplicate samples at each time point (0.5, 1, 2, 4 ,6, 24 and 30 h)..	Was the timing and frequency of sampling adequate?	**1**
Analytical method and measurements of test substance to verify presence in test system	D4 concentrations in soil and aqueous phases determined by solvent extraction/GC-MS and headspace solvent micro-extraction/GS-MS, respectively. Internal standard calibration for both methods. QC samples met established criterion for accuracy.	Were appropriate methods of analysis used?	**1**
Results			
Confounding variables	Hydrolysis expected at higher pH but did not significantly impact the Kd determination. Demonstrated adsorption to test vessel not significant	What sources of variability were noted and did they affect the outcome assessment? Conducted a side experiment to examine hydrolysis kinetic and a vessel adsorption experiment to show little adsorption onto vessel.	**1**
Outcomes unrelated to exposure	none	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**1**
Data	Range of log Koc for absorption was 4.17 – 4.27 with overall average of 4.22; for desorption, 4.23 – 4.39, with average of 4.30.	Were the data appropriately reported to document the outcome(s)? Detailed tables and figures.	**1**
Statistical method and kinetic calculations	To-tailed t-test to verify attainment of equilibrium. Isotherms well described by Freundlich equation (all r^2 >0.998).	Were statistics and/or kinetic calculations described and consistent?	**1**
Plausibility of results	Results indicate strong affinity to sorb to soil with partitioning to soil organic matter influential. The linear isotherms and the general agreement in the Koc values across the different soils suggested that partitioning into soil organic matter dominated the overall sorption of D4 from water. The comparable values of log Koc for adsorption and desorption indicated that the sorption of 13C-D4 was largely reversible for short contact times (ca. 48 h)	Were the study results reasonable?	**1**
		Score (17-68):	**19**

Short citation (Author, year, or ID)	**KOZER14A**		
Full citation (or link)	**Kozerski, GE, S Xu, J Miller and J Durham. 2014. Determination of soil-water sorption coefficients of volatile methlysiloxanes. Environ Toxiocl. Chem 33(9); 1937-1945**		
Study type (e.g., OECD Guideline if applicable)	**Published article on study DOWCO07B; not summarized here in detail**		
Study director (if applicable)	**N/A**		
GLP compliance (Y/N)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Description: The study concluded that, compared to traditional hydrophobic organic compounds, Koc values for cVMS are significantly lower than expected based on Kow. A linear free energy relationship analysis showed that these differences could be rationalized quantitatively in terms of the inherent characteristics of the VMS compounds, combined with the differences in solvation properties of organic matter and octanol. **Remarks:** This article may be consulted during preparation of the ecological risk assessment for D4 to show differences in BMF and TMF values when assessed with the elimination half-life method compared to standard methods used to calculate BMF and TMF. The sponsor study version of this paper, DOWCO07B, will also be consulted during reparation of the ecological risk assessment for D4.			

Short citation (Author, year, or ID)	**PANAG15A**		
Full citation (or link)	**Panagopoulos, D., A. Jahnke, A. Kierkegaard, and M. MacLeod. 2015. Organic carbon/water and dissolved organic carbon/water partitioning of cyclic volatile methylsiloxanes: measurements and polyparameter linear free energy relationships. *Environmental Science & Technology 49*(20): 12161–12168.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	Sigma-Aldrich, purity information not provided	Was the source and purity identified? Source was identified, not purity	**2**
Test Design			
Test system	Purge and trap system equilibrium method using a closed system and measured by GC.	Were appropriate methods used? Indirect method, not comparable to guideline	**3**
Test conditions	Field sediment collected from freshwater lake and spiked; added to system and added to a continuously stirred volume of water in the purge and trap system. Head space continually purged. Purged material collected in a solid-phase extraction column. Measurements occurred at 2, 4, 8, 12, 24, 48, and 72 hours.	Were the test conditions appropriate? Indirect method, not comparable to guideline	**3**
Methods and Observations			
Analytical or other methods described	1,4-dichlorobenzene and a-hexachlorocyclohexane used to calibrate mass transfer coefficients, three PCBs used as reference materials. Blanks run, standards renewed once per month. Method detection limits and method quantification limits calculated.	Was the test substance analytically verified in the test system using appropriate methods? Yes	**2**
Results			
Findings described	Measured partitioning between organic carbon and water (Koc) and dissolved organic carbon and water (Kdoc) Log Koc 5.06 ± 0.08; Log Kdoc 5.05 ± 0.07. Measurements of Koc were made using sediment as the organic carbon source which could account for difference in log Koc compared to other studies	Were the findings consistent with the methodology? Yes, but use of sediments likely affected Koc determinations.	**2**
		Score (6–24):	**13**

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Bioaccumulation reviews

Short citation (Author, year, or ID)	**WOODB13A**		
Full citation (or link)	**Woodburn, K., K. Drottar, J. Domoradzki, J. Durham, D. McNett, and R. Jezowski. 2013. Determination of the dietary biomagnification of octamethylcyclotetrasiloxane and decamethylcyclopentasiloxane with the rainbow trout (*Oncorhynchus mykiss*). *Chemosphere* 93(5): 779–788.**		
Study type (e.g., OECD Guideline if applicable)	**Yes – U.S. EPA OPPTS Ecological Effects Test Guidelines Series 850. Guideline 850.1730 and OECD Test No. 305: Bioconcentration: Flow-through Fish Test**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4 and D5	Was the test substance identified definitively? Yes, CAS numbers were provided.	**1**
Composition (purity, origin); single substance (not mixture)	Origin: not provided Purity: D4 and D5 purity not provided. 14C-uniformly radiolabeled D4 and D5, with specific activities of 6.5 and 6.1 mCi g-1, respectively, and radiochemical purities of 99.1% and 98.7%, respectively		**2**
Preparation	Spiked food preparation for each test material consisted of preparing feed at a nominal concentration of 500 µg/g feed; D4 or D5 was added directly to fish food – no solvents were used in the spiking procedure due to the low surface energy properties of the cVMS chemicals. The spiked feed was then mixed overnight (~15 h) using a Fisher roto-rack. Control food consisted of untreated trout chow. When not in use, both spiked and control feed were stored in a refrigerator.	Was the test substance preparation described and appropriate for the test system? Yes.	**1**
Test Design			
Test system (suitability)	Trout were fed at a rate of 3% of the mean wet weight of the trout per day, corrected for weight gain after each sampling d. Fish were allowed to feed for 1 h following food administration. Uneaten food, if any, was then immediately siphoned from the tank to minimize aqueous 14C-D4 or 14C-D5 bioconcentration across the fish gills and skin. During the experiment, there was no observed leftover food remaining in either aquarium for removal. The trout were fed once daily during the experiment. Trout were maintained in a continuous flow diluter system. Flow rates were adjusted to provide approximately 10 volume additions per day to each replicate. The test chambers were 57-L polyethylene aquaria containing approximately 42-L of water.	Was the test method appropriate for the test substance? Yes	**1**

Short citation (Author, year, or ID)	**WOODB13A**		
Full citation (or link)	**Woodburn, K., K. Drottar, J. Domoradzki, J. Durham, D. McNett, and R. Jezowski. 2013. Determination of the dietary biomagnification of octamethylcyclotetrasiloxane and decamethylcyclopentasiloxane with the rainbow trout (*Oncorhynchus mykiss*). *Chemosphere* 93(5): 779–788.**		
Study type (e.g., OECD Guideline if applicable)	**Yes – U.S. EPA OPPTS Ecological Effects Test Guidelines Series 850. Guideline 850.1730 and OECD Test No. 305: Bioconcentration: Flow-through Fish Test**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test conditions (monitored and appropriate)	35 day exposure period with food concentration of 500 µg/g of D4 or D5, followed by non-exposure phase of 42 days with clean food. Lighting used to illuminate the test chambers was provided by cool white fluorescent bulbs with a photoperiod of 16 h light and 8 h dark; measured light intensity ranged from 41 to 48 foot-candles at the surface of the water. The test chambers were placed in a temperature-controlled water bath set to maintain a temperature of 12 ± 2 °C. Water temperature, flow rate, dissolved oxygen (DO), and pH were monitored on a daily basis from both the exposure and control aquaria. In addition, the aquaria were cleaned to remove uneaten food at 1 h post-feeding, in addition to cleaning as needed	Were test conditions appropriate? Yes	**1**
Consistency (across groups)	Similar size/age rainbow trout used in control and exposure group. Laboratory testing conditions by use of various QA methods created consistency.	Were test conditions consistent across groups? Yes	**1**
Test organisms (if applicable)	Rainbow trout (***Oncorhynchus mykiss*****).** Fish were juvenile trout with an initial wet weight (mean ± standard deviation) of 1.18 (±0.16) and 1.36 (±0.29) g (wet weight, ww) for D4 and D5 studies, respectively, and 4–6 cm in length. Trout were indiscriminately assigned to test chambers at test Initiation. Two replicate test chambers were maintained in each treatment group, with 70 rainbow trout in each test chamber, for a total of 140 trout per treatment.	Was the inoculum or test organism appropriate? Yes	**1**
Controls	Control fish were fed identical trout chow without test material. 70 rainbow trout used in control; no two aquaria replicates for the control.	Were the appropriate controls used? Yes	**1**
Duration	77 days	Was the duration of the study appropriate? Yes	**1**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Biomagnification factor (BMF); lipid-adjusted-BMF (BMF(L)), elimination half-life for D4 and D5. Daily observations of	Were the appropriate outcomes reported? Yes	**1**

Short citation (Author, year, or ID)	**WOODB13A**		
Full citation (or link)	**Woodburn, K., K. Drottar, J. Domoradzki, J. Durham, D. McNett, and R. Jezowski. 2013. Determination of the dietary biomagnification of octamethylcyclotetrasiloxane and decamethylcyclopentasiloxane with the rainbow trout (*Oncorhynchus mykiss*). *Chemosphere* 93(5): 779–788.**		
Study type (e.g., OECD Guideline if applicable)	**Yes – U.S. EPA OPPTS Ecological Effects Test Guidelines Series 850. Guideline 850.1730 and OECD Test No. 305: Bioconcentration: Flow-through Fish Test**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	mortality and other clinical signs were made. Temperature was monitoring continuously and dissolved oxygen was monitored daily.		
Control performance	Fish weight and %lipid concentrations in control fish were compared to test fish.	Was control performance acceptable? No guidelines provided on acceptable control performance.	**3**
Sampling adequacy (frequency, duration)	Fish were sacrificed at selected intervals for measurement of total 14C activity and parent D4 or D5 in tissue. Three trout were collected from each replicate chamber (N = 6) on day 1, 3, 7, 10, 14, 21, 28, and 35 of the exposure phase and day 1, 2, 4, 7, 14, 28, and 42 of the depuration phase. Fish feed and whole fish tissue was sampled immediately prior to test initiation to determine lipid content. Feed was analyzed for either D4 or D5 immediately prior to test initiation and on four other regularly scheduled sampling day through the exposure phase of the study (e.g., day 14, 23, 30, and 37 for the D5 test). The whole fish carcass (minus digestive tract), the digestive tract and its contents, and fish liver tissue (D4 only) were analyzed separately for both total 14C activity and parent D4 or D5 concentrations. Aquarium water (triplicate, 10 mL, mid-depth) was sampled daily during exposure (day 0–35) for total aqueous 14C activity,	Was the timing and frequency of sampling adequate? Yes	**1**
Analytical method and measurements of test substance to verify presence in test system	Lipid content was determined using a chloroform extraction/gravimetric method (Randall et al., 1991). Four fish were extracted for the day 0 analyses, while four exposure and four control fish (N = 8) were analyzed for each of the subsequent lipid determinations during the uptake and depuration periods. Fish liver tissue was collected during the depuration period and analyzed qualitatively for the distribution of parent D4 and metabolites via high-performance liquid chromatography (HPLC) with radiochemical detection.	Were appropriate methods of analysis used? Yes	**1**

Short citation (Author, year, or ID)	WOODB13A		
Full citation (or link)	Woodburn, K., K. Drottar, J. Domoradzki, J. Durham, D. McNett, and R. Jezowski. 2013. Determination of the dietary biomagnification of octamethylcyclotetrasiloxane and decamethylcyclopentasiloxane with the rainbow trout (*Oncorhynchus mykiss*). *Chemosphere* 93(5): 779–788.		
Study type (e.g., OECD Guideline if applicable)	Yes – U.S. EPA OPPTS Ecological Effects Test Guidelines Series 850. Guideline 850.1730 and OECD Test No. 305: Bioconcentration: Flow-through Fish Test		
Study Director (if applicable)	N/A		
GLP Compliance (if applicable)	N/A		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	The concentrations of D4 and D5 in trout chow were determined by gas chromatography/flame ionization detection (GC/FID), following organic solvent extraction with hexane. Feed samples were analyzed by GC/FID. Individual fish samples (whole fish minus GI tract, plus digestive tract samples) and fish liver samples (D4 only) were homogenized and extracted (2:1 ratio) with tetrahydrofuran (THF) prior to analysis via gas chromatography/mass spectrometry (GC/MS). A total of six exposure fish and one control fish were processed per sampling date and analyzed for parent chemical and total 14C activity. Total radioactivity was quantified in the THF extracts of fish and digestive tract by direct analysis using a liquid scintillation counter (LSC).		
Results			
Confounding variables	The choice of the 500 µg/g dose level for D4 and D5 was selected in collaboration with the UK Risk Assessment Task Force and was considered to be a good compromise to address concerns about analytical detection limits and the risk of overdosing the trout. For each trout, the gastrointestinal (GI) or digestive tract was removed prior to whole fish homogenization and chemical analysis, to avoid analytes in undigested food.	What sources of variability were noted and did they affect the outcome assessment? Confounding variables were listed and described in detail to provide rationale for specific methods that were used to address the variables. No mention on measures taken to prevent contamination or volatilization during sampling.	**2**
Outcomes unrelated to exposure	None mentioned.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)?	**-**
Data	Water and fish tissue samples were collected at selected intervals throughout the study for measurement of total 14C activity and parent D4 and D5. Tissue and feed concentrations were used to determine both empirical and kinetic BMF values for D4 and D5 in rainbow trout.	Were the data appropriately reported to document the outcome(s)? Yes, though no raw data was reported.	**2**

Short citation (Author, year, or ID)	**WOODB13A**		
Full citation (or link)	**Woodburn, K., K. Drottar, J. Domoradzki, J. Durham, D. McNett, and R. Jezowski. 2013. Determination of the dietary biomagnification of octamethylcyclotetrasiloxane and decamethylcyclopentasiloxane with the rainbow trout (*Oncorhynchus mykiss*). *Chemosphere* 93(5): 779–788.**		
Study type (e.g., OECD Guideline if applicable)	**Yes – U.S. EPA OPPTS Ecological Effects Test Guidelines Series 850. Guideline 850.1730 and OECD Test No. 305: Bioconcentration: Flow-through Fish Test**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	Results Summary: The fish tissue concentrations of D4 and D5 achieved empirical steady-state by day 21 in each study. Elimination half-lives of approximately 20 d. BMF and BMF(L) values of 0.28 and 0.66 for D4, respectively, and 0.32 and 0.85 for D5, respectively. Growth-corrected depuration rate constants modeled over the entire study data set indicated slower elimination kinetics for D4 (k2 of 0.007 d-1 or half-life of 100 d) compared to D5 (k2 of 0.010 d-1 or elimination half-life of 69 d). Kinetic BMFk values (i.e., k1/k2) for D4 and D5 were 1.7 and 1.3, respectively, with lipid-adjusted BMFk(L) values of 4.0 and 3.4, respectively.		
Statistical method and kinetic calculations	Tissue concentrations of parent D4 or D5 were evaluated for normality and homogeneity of variance using Shapiro–Wilk's test and Bartlett's test, respectively. Tissue concentrations were then evaluated using analysis of variance (ANOVA). All statistics for determination of steady-state were performed using TOXSTAT version 3.5 software. Method validation: Validated methods for D4 and D5 were based on calibrating a GC/MS using spiked solvent standards in THF and running extracts of spiked whole fish samples and blank fish samples against the calibration curve; control fish were used for the spiked recoveries. Extractions of fish spikes were done with THF containing the internal standards M4Q (D5) or 13C-D4 (D4), as appropriate.	Were statistics and/or kinetic calculations described and consistent? Yes	**1**
Plausibility of results	Various standards and method validations used for samples and analytical methods.	Were the study results reasonable? Yes	**1**
		Score (18–72); without one criterion, possible score was 17–68:	**22**

Short citation (Author, year, or ID)	**XUE18A**		
Full citation (or link)	**Xue, X., H. Jia, and J. Xue. 2018. Bioaccumulation of methyl siloxanes in common carp (*Cyprinus carpio*) and in an estuarine food web in Northeastern China. Archives of Environmental Contamination and Toxicology: 1-12.**		
Study type (e.g., OECD Guideline if applicable)	**Peer-reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, and D6	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	Origin: Tokyo Chemical Industry (Wellesley Hill, MA) Purity: no details provided	Was the source and purity identified? No information on purity	**2**
Preparation	For the common carp experiments, D4 was added to aquaria water and was stirred for 30 min. Prepared D4 water rested for 1 day before being added to the aquaria. Additional supplements of the same concentration of D4 water was added to the carp aquaria every two days during the experiment. Fish were wrapped in clean aluminum foil and frozen at -40C for 10 min before dissection. Muscle tissue was subsampled for chemical analysis, but method used to subsample was not described. Use of personal care products was not allowed. Water was extracted and analyzed for siloxanes by gas chromatography-mass spectrometery (GCMS). For the food web study, zooplankton, and 12 aquatic species of invertebrates and vertebrates were collected from a food web in Shuangtaizi estuary in northeastern China and concentrations of methyl siloxanes in these species were determined. Zooplankton were collected by net (0.096 mm mesh). Invertebrates and fish were collected as described in Ma et al. (2013); this paper wasn't reviewed. All samples were packed in solvent washed aluminum foil and frozen immediately and stored in the lab at -20C. Muscle tissue of invertebrate and fish samples were subsampled, but method used to subsample was not described. Samples were analyzed by gas chromatography-mass spectrometry (GCMS). Person care products were not allowed.	Was the test substance preparation described and appropriate for the test system? Yes but some details lacking.	**2**
Test Design			

Short citation (Author, year, or ID)	**XUE18A**		
Full citation (or link)	**Xue, X., H. Jia, and J. Xue. 2018. Bioaccumulation of methyl siloxanes in common carp (*Cyprinus carpio*) and in an estuarine food web in Northeastern China. Archives of Environmental Contamination and Toxicology: 1-12.**		
Study type (e.g., OECD Guideline if applicable)	**Peer-reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test system (suitability)	Labaquaria with supplemental D4 water added for common carp exposure tests. For the food web tests, freshwater and marine biological samples were collected from an estuary near the Bohai Sea, China in October 2014.	Was the test method appropriate for the test substance? Yes; however, no details were provided on the exposure concentrations use for cVMSs or methods used for prevention of volatility during testing. Not stated if aquaria were closed to prevent volatile test compounds from escaping.	**3**
Test conditions (monitored and appropriate)	Common carp exposure tests (for assessing bioconcentration factor value): Duration: 32 days for uptake phase, 32 days for depurination phase Vessel: glass aquaria, highly aerated (>90% DO throughout the experiment) Test organisms: 50 fish Food: not fed during 64 day experiment Food web tests: Samples collected from estuary and analyzed in lab. Collected samples included: Fish: yellow goosefish (*Lophius litulon*) (n=30) marked lancettailgoby (*Chaemrichthys stigmatias*) (n=13) joyner's tonguesole (*Arelicus joyneri gunther*) (n=12) Invertebrates: neverita albumen (*Glossaulax didyma*) (n=7) Japanese stone crab (*Charybdis japonica*) (n=3) swimming crab (*Portunus trituberculatus*) (n=1) ark shell (*Scapharca subcrenata*) (n=1) Japanese snapping shrimp (*Alpheus japonicus*) (n=3) Chinese ditch prawn (*Palaemon graviera*) (n=2) Chinese white shrimp (*Fenneropenaeus chinensis*) (n=2) Japanese mantis shrimp (*Oratosquilla oratoria*) (n=14)	Were test conditions appropriate? Samples sizes, weight, and length provided for all samples. However, sample sizes were not consistent across species, and number of replicate test aquaria used in the carp exposure was not clearly stated. Lack of feeding during the 64-day carp study resulted in a loss of weight over the course of the study, which could have altered uptake, elimination and metabolic responses of the test species.	**4**

Short citation (Author, year, or ID)	**XUE18A**		
Full citation (or link)	**Xue, X., H. Jia, and J. Xue. 2018. Bioaccumulation of methyl siloxanes in common carp (*Cyprinus carpio*) and in an estuarine food web in Northeastern China. Archives of Environmental Contamination and Toxicology: 1-12.**		
Study type (e.g., OECD Guideline if applicable)	**Peer-reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	Plankton: zooplankton (n=3)		
Consistency (across groups)	. Preliminary experiments found that after 4 days, organosiloxane concentrations were below detection limits. Therefore, supplemental organosiloxane pre-mixed with water was added to the aquaria every two days to maintain a steady level of the organosiloxane.	Were test conditions consistent across groups? Yes	**1**
Test organisms (if applicable)	Common carp exposure tests: Species: Common carp (*Cyprinus carpio*) Age: 1 year Size: similar Visual observation: excellent physical condition Food: no food during exposures Food web exposure tests: 12 vertebrates and invertebrates in Shuangtaizi estuary for assessing for food chain transfer (TMF)	Was the inoculum or test organism appropriate? Yes. Fish were obtained from a local fish market. Data on concentrations of siloxanes in fish at time = 0 or before the start of the experiment were not presented.	**1**
Controls	Personal care products not used during sampling and laboratory analyses. PE gloves used. All glassware washed with acetone and hexane. Plastic products used minimally. Sample pretreatment was conducted in clean air cabinet and amount of time needed for preparation was reduced as much as possible to avoid volatilization. All appliances, equipment, and solvents checked for contamination. Instrumental contamination check performed with isooctane injection. All samples spiked with labeled recovery standards. Procedural blanks and matrix spikes used and analyzed in each batch of ten samples.	Were the appropriate controls used? Yes; however, limited information was provided on the number or replicates and the determination of the limit of detection (LOD) and limit of quantitation (LOQ).	**1**
Duration	Common carp tests: 64 days (two phases) Food web tests: Not relevant to this study. Sampling was a one-time event rather than a time series monitoring study.	Was the duration of the study appropriate? Yes	**1**
Methods and Observations			

Short citation (Author, year, or ID)	**XUE18A**		
Full citation (or link)	**Xue, X., H. Jia, and J. Xue. 2018. Bioaccumulation of methyl siloxanes in common carp (*Cyprinus carpio*) and in an estuarine food web in Northeastern China. Archives of Environmental Contamination and Toxicology: 1-12.**		
Study type (e.g., OECD Guideline if applicable)	**Peer-reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Observations (half-lives, coefficients, etc.)	Bioconcentration factor (BCF) (carp experiments) Trophic magnification factor (TMF) (food web exposure experiments) Biomagnification factor (BMF) (food web exposure tests)	Were the appropriate outcomes reported? Yes, but units unclear. Also, TMF was calculated only based on one food chain in the food web and the sample sizes of the biota were small.	**2**
Control performance	Average analytical recoveries: 110 ± 13% (D5) for biota samples. Additional recovery information not provided.	Was control performance acceptable? No, not all recovery information was provided.	**2**
Sampling adequacy (frequency, duration)	Common carp exposure tests: During uptake phase of test, fish and water samples collected on days 1, 2, 3, 4, 6, 8, 10, 16, 24, and 32. During depuration phase, fish and water samples collected on days 40, 48, 56, and 64. Three fish and three 1L water samples were collected during each collection event. Unclear if samples of fish and water were collected at each time point from replicate aquaria or from a single aquarium. Collected fish weighed and measured (length) and dissected for muscle tissue. Food web exposure tests: Study refers to previously published methods used for collection of biological samples. Zooplankton collection was based on HY003.4-91 method Samples packed and transported to laboratory and stored in -20 °C. Muscle tissues collected: for fish the entire muscle was collected and for invertebrates, muscle collected from specific areas. Body length and weight recorded.	Was the timing and frequency of sampling adequate? Yes	**1**

Short citation (Author, year, or ID)	**XUE18A**		
Full citation (or link)	**Xue, X., H. Jia, and J. Xue. 2018. Bioaccumulation of methyl siloxanes in common carp (*Cyprinus carpio*) and in an estuarine food web in Northeastern China. Archives of Environmental Contamination and Toxicology: 1-12.**		
Study type (e.g., OECD Guideline if applicable)	**Peer-reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Analytical method and measurements of test substance to verify presence in test system	Water and biological samples underwent extraction and underwent GC-MS. stable nitrogen (15N) and stable carbon (13C) isotope analyses were performed on muscle tissue samples to determine trophic levels.	Were appropriate methods of analysis used? Yes, however LOD and LOQ not well-defined	**2**
Results			
Confounding variables	Contamination and volatilization are important confounding factors.	What sources of variability were noted and did they affect the outcome assessment? Data on background concentrations of siloxanes in carp before the start or the experiment were not provided Several measures were taken to prevent contamination and volatilization during sampling. Field samples were taken back to the laboratory for processing.	**1**
Outcomes unrelated to exposure	None mentioned.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)? Not applicable	**-**
Data	Yes, raw data tables provided in the SI. Not all data presented. <u>Results summary</u>: BCF for D4: 6,197 L/kg indicating strong bioaccumulation potential in common carp. The highest concentration in common carp of D4, D5, D6, and D7 was observed in the 32nd day in the uptake phase (29.4 ± 3.17, 38.2 ± 3.68, 27.6 ± 2.29, 1.90 ± 0.15 ng/g dw). The final concentrations of D4, D5, D6, D7, and L10 in the muscle tissue of common carp were 4.40 ± 0.85, 10.3 ± 2.99, 3.29 ± 0.82, 0.49 ± 0.13, and 2.60 ± 0.41 ng/g dw, respectively.	Were the data appropriately reported to document the outcome(s)? Not all data presented. Concentration data were reported on a dry weight basis and BCF values were reported on a wet weight basis, but the solid content of the fish was not reported.	**2**

Short citation (Author, year, or ID)	**XUE18A**		
Full citation (or link)	**Xue, X., H. Jia, and J. Xue. 2018. Bioaccumulation of methyl siloxanes in common carp (*Cyprinus carpio*) and in an estuarine food web in Northeastern China. Archives of Environmental Contamination and Toxicology: 1-12.**		
Study type (e.g., OECD Guideline if applicable)	**Peer-reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	During the 32 days of uptake, concentrations of D4, D5, D6, D7, and L10 in the aquaria water ranged from 3.35–7.58 (4.79 ± 1.19), 21.3–34.9 (26.3 ± 5.03), 20.2–38.8 (24.6 ± 0.86), 2.21–4.83 (3.28 ± 1.45), and 8.13–18.2 (12.9 ± 3.08) ng/L, respectively. The BMF values for D4, D5, D6, L7, L8, L9, and L10 were calculated as follows: 3.2, 5.2, 9.0, 11, 9.2, 3.4, and 2.2. Trophic magnification was not found for D4 in any food chain selected for this study. TMFs for D5, D6 and L7-10 ranged from 3.0 to 11.		
Statistical method and kinetic calculations	Details provided for calculating BCF, BMF, and TMF. Limits of detection and limit of quantification determined. For the calculation of arithmetic mean and standard deviation (SD), nondetects were substituted with half of the LOQ. Coefficients of determination ($R2$) used to describe the goodness of fit of a model. Relationships between concentrations of methyl siloxanes in the muscle tissue of common carp and collection time during clearance phase were also fitted. The concentrations of methyl siloxanes were log-transformed before calculating the TMF values.	Were statistics and/or kinetic calculations described and consistent? Equations used to calculate the uptake and depuration rates are not well-aligned with the measured data.	**3**
Plausibility of results	Paper refers to Jai et al. (2015) for many of the methods used. Jai et al. (2015) is another paper reviewed for the environmental fate topic. Steps taken to prevent siloxane contamination of samples from other sources such as personal care products. Blanks used. Numerous quality control steps described.	Were the study results reasonable? Yes, however, the lack of feeding during the 64-day carp study resulted in a loss of weight over the course of the study, which could have altered uptake, elimination and metabolic responses of the test species. Feeding organisms during exposure studies is standard practice and this may present some bias in the results.	**3**
		Score (18–72); without one criterion, possible score was 17-68:	**32**

Short citation (Author, year, or ID)	**BORGA12A**		
Full citation (or link)	**Borgå K, Fjeld E, Kierkegaard A, McLachlan MS. 2012. Food Web Accumulation of Cyclic Siloxanes in Lake Mjøsa, Norway. Environmental Science & Technology 46:6347−6354.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for biomagnification/trophic magnification**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, and D6	Was the test substance identified definitively? No, samples were from the field. However, radiolabeled surrogate standards were used, and internal matrix control (herring homogenate) was used to verify cVMS concentrations.	**2**
Composition (purity, origin); single substance (not mixture)	Source: Not applicable; this is a field study Purity: Not applicable; this is a field study Single substance: Not applicable; this is a field study	Was the source and purity identified? No, samples were from the field. However, radiolabeled surrogate standards were used, and internal matrix control (herring homogenate) was used to verify cVMS concentrations.	**2**
Preparation	cVMS concentrations were determined from field samples and not prepared in the lab. Zooplankton and mysis samples were collected by trawling at with 250 µm nets and put in glass jars. Fish were collected by gill nets and samples were stored frozen whole until sample preparation and analysis. Fish were filleted outdoors to avoid indoor air contamination. Samples were prepared outdoors to avoid contamination. All large surfaces for sampling was covered in pre-cleaned aluminum foil. Study personnel avoided using personal care products 24 hr prior to field work. Radiolabeled surrogate standards were used, and internal matrix control (herring homogenate) was used to verify cVMS concentrations.	Was the test substance preparation described and appropriate for the test system? Substance preparation did not occur, but handling and storage of samples for cVMS analysis is more applicable and that was appropriately given the concerns for contamination. In addition, surrogate standards and internal matrix control were used.	**2**
Test Design			
Test system (suitability)	Field collection of representatives of the pelagic food web at Lake Mjøsa in September-October 2010, followed by lab analysis.	Was the test method appropriate for the test substance? Yes, Lake Mjøsa is the largest lake in Norway and has intensive agriculture and some industrial activity and the lake has a long history of pollution by legacy organic contaminants. This lake's food web is well studied and has been monitored for several years.	**1**

Short citation (Author, year, or ID)	**BORGA12A**		
Full citation (or link)	**Borgå K, Fjeld E, Kierkegaard A, McLachlan MS. 2012. Food Web Accumulation of Cyclic Siloxanes in Lake Mjøsa, Norway. Environmental Science & Technology 46:6347−6354.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for biomagnification/trophic magnification**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test conditions (monitored and appropriate)	Data included representatives of the pelagic food web in this lake. Whole samples of zooplankton (epilimnion, hypolimnion, and mysis), and muscle samples of fish (vendace, smelt and trout) were analyzed for stable isotopes, cVMS, lipid content, and select PCB and BDE congeners for comparison to cVMS.	Were test conditions appropriate? This is a field study, so the conditions were appropriate. The pelagic food web had been monitored for several years.	**1**
Consistency (across groups)	Laboratory testing conditions by use of various QA methods created consistency.	Were test conditions consistent across groups? Similar sample sizes were collected for zooplankton (n=4 for each zooplankton type) and fish (n=5 for each fish).	**1**
Test organisms (if applicable)	Species: Epilimnion zooplankton (predominantly water fleas *Daphnia galeata*), n = 4 pooled samples; hypolimnion zooplankton (predominantly copepods *Limnocalanus macrurus*), n=4 pooled samples; mysis, n = 4 pooled samples Fish: Vendace (*Coregonus albula*) n = 5 pooled samples of 2-3 individuals Smelt (*Osmerus eperlanus*), n = 5 pooled samples of 2-3 individuals Brown trout *(Salma trutta)* n = 5 individuals. Age: not determined Physical measurements: fresh weight, total length cVMS and Stable isotope analysis: whole samples of zooplankton; muscle of fish Health/Handling: No health observations provided. Acclimation was not relevant to the study.	Was the inoculum or test organism appropriate? Yes, this pelagic food web had been previously characterized and monitored for several years. However, sample size seemed small for the large size of the lake system. In addition, only muscle of the fish, not whole-body samples were analyzed for cVMS concentrations.	**3**
Controls	Field blanks, radio-labeled surrogates for cVMS, procedural blanks, internal matrix control (herring homogenate). Three of the brown trout and two of the vendace samples were analyzed in duplicate. cVMS results were not blank corrected.	Were the appropriate controls used? Yes. However, these methods and controls are not standardized, nor have they been validated.	**2**

Short citation (Author, year, or ID)	**BORGA12A**		
Full citation (or link)	**Borgå K, Fjeld E, Kierkegaard A, McLachlan MS. 2012. Food Web Accumulation of Cyclic Siloxanes in Lake Mjøsa, Norway. Environmental Science & Technology 46:6347−6354.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for biomagnification/trophic magnification**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Duration	Not relevant to study.	Was the duration of the study appropriate? Characterization of cVMS in environment was from one time point only, not designed as a long-term monitoring study.	**-**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Concentrations of cVMS on a lipid normalized basis, stable isotopes 13C and 15N, and trophic magnification factors (TMFs) = slope of the lipid normalized cVMS concentration regressed onto the trophic level (based on stable isotope data).	Were the appropriate outcomes reported? Methodology was appropriate to report outcomes of interest. More samples should have been considered before proceeding with study. While this paper did not calculate TMFs for D4; the ECHA dossier provides TMFs from 0.6 to 1.3 for this study using a probabilistic assessment conducted by Dow Corning. These calculated TMFs suggest that D4 does not exhibit trophic biomagnification.	**2**
Control performance	Control herring homogenates showed good agreement with previous analysis. However, the difference between field blanks and samples for D4 was below a ratio (sample/field blank) of 5 in 22 of 32 samples. The mean difference in duplicate samples for trout and vendace was 23%. This could be due to the samples not be homogenized to avoid risk of contamination. Thus, samples were not corrected for background levels.	Was control performance acceptable? No, while multiple controls were used as QA measures (field blank and matrix interference), some of the results of the field blanks for D4 were very close to the results for the biota samples from the field.	**3**
Sampling adequacy (frequency, duration)	Field sampling occurred during 1 period. Only 4 to 5 samples of each trophic level were collected.	Was the timing and frequency of sampling adequate? No, only 4 to 5 samples of each trophic level were collected; this seems low given the size of the lake system and the possible variability in D4 concentrations in field samples. This study was only conducted over 1 sampling period.	**3**
Analytical method and measurements of test substance to verify presence in test system	cVMS were analyzed by a purge and trap method developed by this group followed by gas chromatography/mass spectrometry (GC/MS). The purge and trap method was later refined by Borgå et al. (2013) because it appeared to be less reliable than other methods. PCBs and PBDEs were analyzed with established methods in Norway. Stable isotopes of N and C were analyzed with established methods in Norway. Stable	Were appropriate methods of analysis used? Details were provided on origin of reference materials for field blanks and internal matrix (herring homogenate). The cVMS extraction method was less reliable than other methods. In addition, D4 results for many samples were below the limit of quantification.	**3**

Short citation (Author, year, or ID)	**BORGA12A**		
Full citation (or link)	**Borgå K, Fjeld E, Kierkegaard A, McLachlan MS. 2012. Food Web Accumulation of Cyclic Siloxanes in Lake Mjøsa, Norway. Environmental Science & Technology 46:6347−6354.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for biomagnification/trophic magnification**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	isotopes of N and C were analyzed using standard protocols. Borgå K, Fjeld E, Kierkegaard A, McLachlan ME. 2013. Consistency in Trophic Magnification Factors of Cyclic Methyl Siloxanes in Pelagic Freshwater Food Webs Leading to Brown Trout. Environmental Science & Technology 47:14394−14402.		
Results			
Confounding variables	Contamination and volatilization are important confounding factors for D4 studies.	What sources of variability were noted and did they affect the outcome assessment? Several measures were taken to prevent contamination during sampling. However, samples were processed in the open air and D4 is very volatile.	**3**
Outcomes unrelated to exposure	None mentioned.	Not applicable.	**-**
Data	Raw data tables reported in supplemental information. cVMS data were reported on a wet weight basis in the supplemental information and on a lipid normalized basis in the paper. All D4 values were below the limit of quantification. Results summary: Brown trout muscle tissues contained an average of 190 ng/g lipid weight. Highest measured D4 concentration was 4.5 ng/g wet weight in brown trout. TMFs were not calculated for D4 as too many samples had concentrations below the limit of quantitation (<71 to <150).	Were the data appropriately reported to document the outcome(s)? Yes.	**1**
Statistical method and kinetic calculations	TMF calculations were not made for D4 due to too few samples having detectable concentrations.	Were statistics and/or kinetic calculations described and consistent? Provided details on why all measurements were necessary and how stats were used/selected. This does not apply since TMFs were not calculated for D4 by the authors.	**-**

Short citation (Author, year, or ID)	**BORGA12A**		
Full citation (or link)	**Borgå K, Fjeld E, Kierkegaard A, McLachlan MS. 2012. Food Web Accumulation of Cyclic Siloxanes in Lake Mjøsa, Norway. Environmental Science & Technology 46:6347−6354.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for biomagnification/trophic magnification**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Plausibility of results	All controls well-documented, but concentrations of D4 were below the limit of quantification in many samples leads to uncertainty with the reported data.	Were the study results reasonable? Yes, controls provided plausibility to results. However, this purge and trap extraction method was later refined by Borgå et al. (2013) because it appeared to be less reliable than other methods. In addition, concentrations of D4 were below the limit of quantification in many samples, which leads to uncertainty with the reported data. Larger sample sizes may have increased likelihood of calculating TMFs for D4.	**2**
		Score (18–72); without 3 criteria, possible score was 15–60:	**31**

Short citation (Author, year, or ID)	**BORGA13A**		
Full citation (or link)	**Borgå K, Fjeld E, Kierkegaard A, McLachlan ME. 2013. Consistency in Trophic Magnification Factors of Cyclic Methyl Siloxanes in Pelagic Freshwater Food Webs Leading to Brown Trout. Environmental Science & Technology 47:14394−14402.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for biomagnification/trophic magnification**		
Study Director (if applicable)	**Borgå K (author)**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, and D6	Was the test substance identified definitively? No, samples were from the field. However, radiolabeled surrogate standards were used, and internal matrix control (herring homogenate) was used to verify cVMS concentrations.	**2**
Composition (purity, origin); single substance (not mixture)	Source: Not applicable; this is a field study Purity: Not applicable; this is a field study Single substance: Not applicable; this is a field study	Was the source and purity identified? No, samples were from the field. However, radiolabeled surrogate standards were used, and internal matrix control (herring homogenate) was used to verify cVMS concentrations.	**2**
Preparation	cVMS concentrations were determined from field samples and not prepared in the lab. Zooplankton and mysis (shrimp) samples were collected by trawling at with 250 µm nets and put in glass jars. Fish were collected by gill nets, traps and angling. Fish were fillet outdoors to avoid indoor air contamination. Samples were prepared outdoors to avoid contamination. All large surfaces for sampling was covered in pre-cleaned aluminum foil. Study personnel avoided using personal care products 24 hr prior to field work. Radiolabeled surrogate standards were used, and internal matrix control (herring homogenate) was used to verify cVMS concentrations.	Was the test substance preparation described and appropriate for the test system? Substance preparation did not occur, but handling and storage of samples for cVMS analysis is more applicable and that was appropriately given the concerns for contamination. In addition, surrogate standards and internal matrix control were used.	**2**
Test Design			
Test system (suitability)	Field collection of representatives of the pelagic food web at Lake Mjøsa, Lake Randsfjorden, and Lake Femunden (this last lake is a remote lake) in July-September 2012, followed by lab analysis.	Was the test method appropriate for the test substance? Lake Mjøsa is the largest lake in Norway and has intensive agriculture and some industrial activity and the lake has a long history of pollution by legacy organic contaminants. Lake Mjøsa is considered to be subject to high to moderate human impact based on pollution load estimates, while Lake Randsfjorden is estimated to experience moderate human impact. Lake Femunden is from a remote area with low human impact. The food web in all three lakes are well-studied and characterized. The main difference between them is that Lake Mjøsa has the pelagic shrimp (mysis) and vendace as the planktivorous fish instead of whitefish as found in Lakes Randsfjorden and Femunden. Lake	**1**

		Femunden also have the Arctic char as the top predator along with brown trout.	
Test conditions (monitored and appropriate)	Data included representatives of the pelagic food web in these lakes: whole samples of zooplankton (epilimnion, hypolimnion, and mysis), and muscle samples of fish (vendace, smelt and trout) from Lake Mjøsa; whole samples of zooplankton (epilimnion, hypolimnion), and muscle samples of fish (whitefish, smelt and trout) from Lake Randsfjorden; muscle samples of fish (Arctic char and brown trout) from Lake Femunden. Samples were analyzed for stable isotopes, cVMS, lipid content, and select chlorinated pesticides, PCB congeners and BDE congeners for comparison to cVMS.	Were test conditions appropriate? This is a field study, so test conditions were appropriate. The pelagic food web had been monitored for several years.	**1**
Consistency (across groups)	Sample sizes were collected for zooplankton were 3-4 for each zooplankton type, for fish were 5-9 for each fish, except for Arctic char for which there was only 1 sample collected.	Were test conditions consistent across groups? Similar sample sizes were collected for zooplankton (n=3-4 for each zooplankton type) and fish (n=5-9 for each fish, except for Arctic char for which there was only 1 sample).	**1**
Test organisms (if applicable)	Species: Lake Mjøsa: Epilimnion zooplankton (*Daphnia galeata, Bosmina longispina*), n = 3 pooled samples; Hypolimnion zooplankton (*Limnocalanus macrurus*), n=4 pooled samples; mysis, n = 4 pooled samples; F ish: Vendace (*Coregonus albula*) n = 7 individuals; Small and large smelt (*Osmerus eperlanus*), n = 5 pooled samples of 5-6 individuals; Brown trout *(Salma trutta)* n = 5 individuals. Lake Randsfjorden: Epilimnion zooplankton (*Daphnia galeata, Eudiaptomus gracilis*), n = 4 pooled samples; Hypolimnion zooplankton (*Daphnia galeata, Limnocalanus macrurus, Heterocope appendiculata*), n=3 pooled samples; Fish: Whitefish (*Coregonus lavaretus*) n = 9 individuals; smelt (*Osmerus eperlanus*), n = 5 pooled samples of 5-6 individuals; Brown trout *(Salma trutta)* n = 5 individuals. Lake Femunden: Fish:	Was the inoculum or test organism appropriate? Yes, this pelagic food web had been previously characterized and monitored for several years. However, sample size seemed small for the large size of the lake system. In addition, only muscle of the fish, not whole-body samples were analyzed for cVMS concentrations.	**3**

	Arctic char (*Salvelinus alpinus*), n=1 individual; Brown trout *(Salma trutta)* n = 6 individuals. Age: not determined Physical measurements: fresh weight, total length cVMS and Stable isotope analysis: whole samples of zooplankton; muscle of fish Health/Handling: No health observations provided. Acclimation was not relevant to the study.		
Controls	Field blanks, radio-labeled surrogates for cVMS, procedural blanks, internal matrix control (herring homogenate). cVMS results were not blank corrected.	Were the appropriate controls used? Yes. However, these methods and controls are not standardized, nor have they been validated.	**2**
Duration	Not relevant to study.	Was the duration of the study appropriate? Characterization of cVMS in environment was from one time point only, not designed as a long-term monitoring study.	**-**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Concentrations of cVMS on a lipid normalized basis, stable isotopes 13C and 15N, and trophic magnification factors (TMFs) = slope of the lipid normalized cVMS concentration regressed onto the trophic level (based on stable isotope data) and TMFs were compared statistically among lakes.	Were the appropriate outcomes reported? Methodology was appropriate to report outcomes of interest. More biological samples should have been considered before proceeding with study. D4 TMFs were low: 0.7 (0.5-0.9). Vendace muscle tissues contained a mean of 81 ng/g lipid weight, which was the highest for the different trophic levels.	**2**
Control performance	Control herring homogenates showed good agreement with previous analysis. However, the relative standard deviation was 32% for D4 in the herring matrix. The D4 concentrations exceeded the limit of quantification in 23% of the samples. There was cVMS levels in the Femunden fish that provides evidence that cVMS concentrations measured in the fish samples from the other two lakes were not significantly influenced by cVMS cross-contamination. The difference in the field blanks and biota samples from Lake Mjøsa was low, but 11 of 21 samples had more than 4x higher concentrations than field blank. More samples in Randsfjorden were close to or below the limit of quantification for D4. No samples had D4 levels above the limit of quantification in Femunden (only fish were analyzed).	Was control performance acceptable? No, while multiple controls used as QA measures (field blank and matrix interference), some of the results of the field blanks for D4 were very close to the results for the biota samples from the field.	**3**
Sampling adequacy (frequency, duration)	This study is a follow up to Borgå et al. (2012), which also used Lake Mjøsa, but only reports one sampling period. In addition, the other lakes used in the study were only sampled once, with a low sample size (1 to 9 samples of each trophic level).	Was the timing and frequency of sampling adequate? Yes for Lake Mjøsa, but not for the other two lakes, which were only sampled once. However, few samples were analyzed in both studies (Borgå et al. 2012 and 2013), which seems low given the size of the lake system and the possible variability in D4 concentrations in field samples.	**3**

Analytical method and measurements of test substance to verify presence in test system	cVMS were analyzed by a purge and trap extraction method developed by this group followed by gas chromatography/mass spectrometry (GC/MS). This extraction method was further refined in this study because in previous studies it appeared to be less reliable than other methods. PCBs, chlorinated pesticides, and PBDEs were analyzed with established methods in Norway. Stable isotopes of N and C were methods in Norway. Stable isotopes of N and C were analyzed using standard protocols.	Were appropriate methods of analysis used? Details were provided on origin of reference materials for field blanks and internal matrix (herring homogenate). The cVMS extraction method was refined in this study to improve repeatability and analyte recovery for this method. However, D4 results for many samples were below the limit of quantification.	**3**
Results			
Confounding variables	Contamination and volatilization are important confounding factors for D4 studies.	What sources of variability were noted and did they affect the outcome assessment? Several measures were taken to prevent contamination during sampling. Contamination appeared to be minimal in this study based on the results for the remote lake. Samples were processed in the open air and D4 is very volatile. However, D4 was detected in several samples in the lake with the high human impact factor.	**2**
Outcomes unrelated to exposure	None mentioned.	Not applicable.	**-**
Data	Raw data tables presented in the supplemental information. <u>Results summary:</u> cVMS data were reported on a wet weight basis in the supplemental information and on a lipid normalized basis in the paper. Zooplankton eplimnion was non-detect for D4. Zooplankton hypolimnion D4 mean conc was 36 to 51 ng/g lipid weight. Mysis D4 mean conc was 53 ng/g lipid weight. Vendace D4 mean conc was 81 ng/g lipid weight. Whitefish was non-detect for D4. Smelt D4 mean conc was 17 to 24 ng/g lipid weight. Brown trout D4 mean conc was 16 to 27 ng/g lipid weight. Arctic char was non-detect for D4 (n=1 from the remote lake). D4 TMFs for Lakes Mjøsa and Randsfjorden were 0.7 (0.5-0.9) and did not differ significantly between lakes regardless of whitefish inclusion. However, 66% of the samples were below the limit of quantification for both lakes. Study did not conclude trophic dilution for D4 due	Were the data appropriately reported to document the outcome(s)? Yes. D4 TMFs were low: 0.7 (0.5-0.9). Vendace muscle tissues contained a mean of 81 ng/g lipid weight, which was the highest for the different trophic levels. The ECHA dossier provides TMFs from 0.6 to 0.8 for this study using a probabilistic assessment conducted by Dow Corning. These calculated TMFs suggest that D4 does not exhibit trophic biomagnification.	**1**

	to uncertainty with the non-detect samples, but concluded that if biomagnification of D4 is occurring, it was very low.		
Statistical method and kinetic calculations	Unlike Borgå et al. (2012), TMF calculations were made for D4 and those values were calculated based on regression analysis on the natural logarithm transformed lipid normalized contaminant concentrations.	Were statistics and/or kinetic calculations described and consistent? Provided details on why all measurements were necessary and how stats were used/selected. TMFs appeared to be calculated using appropriate methods. A probabilistic approach could have been used but it would not likely yield very different results.	**2**
Plausibility of results	All controls well-documented, but concentrations of D4 were below the limit of quantification in many samples leads to uncertainty with the reported data.	Were the study results reasonable? Yes, controls provided plausibility to results. However, concentrations of D4 were below the limit of quantification in some samples, which leads to uncertainty with the reported data.	**2**
		Score (18–72); without 2 criteria, possible score was 16–64:	**31**

Short citation (Author, year, or ID)	DOWCO09C		
Full citation (or link)	Dow Corning Corporation. 2009. Trophic dilution of cyclic volatile methylsiloxane (cVMS) materials in a temperate freshwater lake. HES study no: 10771-108. May 18.		
Study type (e.g., OECD Guideline if applicable)	N		
Study Director (if applicable)	Powell, D.E. and K.B. Woodburn (Authors)		
GLP Compliance (if applicable)	N		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, and D6 No details provided on preparation of the isotopically enriched 13C-D4, 13C-D5, and 13C-D6, used as internal standards.	Was the test substance identified definitively? No, samples were from the field. However, internal standards were used to verify cVMS concentrations.	**3**
Composition (purity, origin); single substance (not mixture)	Source: unknown Origin: unknown Purity: unknown cVMS samples were collected from the field.	Was the source and purity identified? Purity and origin are not relevant to the field collected samples. Purity and origin not identified for the radiolabeled cVMSs used in the analytical measurements.	**3**
Preparation	Biological and sediment samples were collected from Lake Pepin, MN, USA. Fish (whole body) were collected in near shore areas of the lake using electrofishing, and measurements included weight, length, and scales were collected to determine age. Small forage fish of similar size were pooled into composite samples. Total of 3 composite samples for shad, 4 composite samples for shiner. Benthic macroinvertebrates were collected using a standard Ponar dredge. Macroinvertebrates were pooled into composite samples by species and transect (n=5 composite samples of midge larvae; n=2 composite samples of mayfly nymphs).Benthic invertebrates and forage fish processed as composites of whole individuals, whereas all other fish were processed as individual whole specimens Surface sediments and associated quality control (QC) samples were collected from 25 locations using a stainless steel mini-box core. On the day of collection, sediment samples and associated QC samples were homogenized in the individual storage bags and sub-	Was the test substance preparation described and appropriate for the test system? Test substance was not prepared. Field samples were collected, thus sampling and handling is more appropriate to assess here. Equipment in direct contact with samples was decontaminated or equipment was thrown away between samples if cleaning was not possible. Field processing was done downwind of the lake to avoid air contamination.	**3**

Short citation (Author, year, or ID)	DOWCO09C		
Full citation (or link)	Dow Corning Corporation. 2009. Trophic dilution of cyclic volatile methylsiloxane (cVMS) materials in a temperate freshwater lake. HES study no: 10771-108. May 18.		
Study type (e.g., OECD Guideline if applicable)	N		
Study Director (if applicable)	Powell, D.E. and K.B. Woodburn (Authors)		
GLP Compliance (if applicable)	N		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	samples collected for characterization analyses and determination of cVMS concentrations. Sediment samples to be analyzed for water, total organic carbon, and organic matter content. Samples undergoing cVMS measurements underwent extractions.		
Test Design			
Test system (suitability)	Lake Pepin, MN, USA. Lake Pepin is 102 km^2 in size, is nearby the twin cities, and serves as a sediment trap and sink for sediment-associated contaminants. Fish samples were collected in September 2007, and sediment and macroinvertebrate samples were collected in May 2008.	Was the test method appropriate for the test substance? Yes, Lake Pepin represents a large freshwater food web impacted by anthropogenic sources of pollution.	**1**
Test conditions (monitored and appropriate)	Field collection of sediment and biological samples. Data included representative samples of biological organisms representing different compartments of the Lake food web such as fish, and macroinvertebrates	Were test conditions appropriate? This is a field study, so test conditions were appropriate. Lake Pepin has been previously characterized in the published literature, and is an appropriate for this study.	**1**
Consistency (across groups)	Shad (n=3 composite samples; composite samples homogenized from 3 – 10 fish) Shiner (n=4 composite samples; composite samples homogenized from 9 – 48 fish) Sediment samples (25 locations) Midge larvae (n=5 composite samples) Mayfly nymphs (n=2 composite samples)	Were test conditions consistent across groups? No, composite samples for shad and shiner were not based on equal counts of fish.	**2**
Test organisms (if applicable)	The food web that was evaluated included surface sediments, 2 benthic macroinvertebrate species (2 genera, 2 families), and 15 fish species (14 genera, 9 families).	Was the inoculum or test organism appropriate? Yes	**1**
Controls	Fish and sediment reference samples were used to determine background cVMS levels. Field blank	Were the appropriate controls used? Yes; concentrations in the blank fish samples were below detection.	**1**

Short citation (Author, year, or ID)	DOWCO09C		
Full citation (or link)	Dow Corning Corporation. 2009. Trophic dilution of cyclic volatile methylsiloxane (cVMS) materials in a temperate freshwater lake. HES study no: 10771-108. May 18.		
Study type (e.g., OECD Guideline if applicable)	N		
Study Director (if applicable)	Powell, D.E. and K.B. Woodburn (Authors)		
GLP Compliance (if applicable)	N		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	samples were also collected for fish (rainbow trout) and reference samples were also used.		
Duration	Not applicable, a one-time sampling event.	Was the duration of the study appropriate? Not applicable, a one-time sampling event.	-
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Relative trophic levels, trophic magnification factor (BMF), predator/prey BMF, bioaccumulation factors (BSAF)	Were the appropriate outcomes reported? Yes	1
Control performance	Concentrations of the cVMS materials in the blank fish were below detection.	Was control performance acceptable? Yes	1
Sampling adequacy (frequency, duration)	Field sampling occurred during 1 period.	Was the timing and frequency of sampling adequate? No, only one sampling event was conducted.	3
Analytical method and measurements of test substance to verify presence in test system	Biological sample analyses included water and lipid content, stable isotope analysis, and analysis of cVMSs. Carbon coulometry analyses used for organic carbon and mineral content of the sediment. Loss on ignition analyses used to determine sediment composition. cVMS analysis included extraction, followed by GC-MS. QA step of extraction solvents containing internal standards were used. Additional QA steps included reference materials were prepared by Dow Corning for the sediment and fish matrices. Analytical methods were developed and validated using reference materials dosed with isotopically labeled 14C-D4, 14C-D5, and 14C-D6. Concentrations of D4, D5, and D6 in the dosed reference materials were determined by radiometric analysis and by GC-MS analysis. Reference sediment	Were appropriate methods of analysis used? Yes, though a variable instrumental blank response was always present for D4, D5, and D6, which made quantification of the cVMS materials difficult in most samples. A measurement issue was identified and a discussion was presented on methods used to address this issue: "The background response could be minimized and stabilized, but not eliminated, by changing the glass injection port liner and rubber septum prior to every analytical run…". Bridges and Solomon (2016) noted the same issue - "Some problems encountered due to instrumental blank variability. For a number of samples values were below or very close to the LOD."	3

Short citation (Author, year, or ID)	DOWCO09C		
Full citation (or link)	Dow Corning Corporation. 2009. Trophic dilution of cyclic volatile methylsiloxane (cVMS) materials in a temperate freshwater lake. HES study no: 10771-108. May 18.		
Study type (e.g., OECD Guideline if applicable)	N		
Study Director (if applicable)	Powell, D.E. and K.B. Woodburn (Authors)		
GLP Compliance (if applicable)	N		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	used for the field blanks and reference samples was used. Live rainbow trout (*Oncorhynchus mykiss)* used for the field blanks and reference samples were purchased from Rainbow Ranch Trout Farm, located in Tawas, MI.		
Results			
Confounding variables	Individual fish were placed into polyethylene food storage bags and transported back to the lab. Contamination was controlled for by cleaning equipment between sampling in the field or using equipment as single use. Field processing was conducted downwind of the lake to avoid air contamination. Methods to control volatilization were not discussed.	What sources of variability were noted and did they affect the outcome assessment? Yes, methods to control contamination were discussed. Samples were processed in the open air and D4 is very volatile.	**1**
Outcomes unrelated to exposure	None mentioned.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)? Not applicable.	**-**
Data	Yes, raw data tables were reported. <u>Summary of results:</u> Benthic detritivores (i.e., *Chironomous* sp. and *Hexagenia* sp.) occupied the lowest trophic level (Trophic level [TL] ~ 2.0) and pelagic piscivores (i.e., largemouth bass and walleye) occupied the highest trophic level (TL ~3.7). Lipid normalized concentrations of D4, D5, and D6 were greatest in the lowest trophic levels and significantly decreased up the food web, with the lowest concentrations being observed in the highest trophic levels. Trophic magnification factors (TMFs) for the three cVMS materials were all < 1 (range 0.1 to 0.3) indicating trophic dilution across the	Were the data appropriately reported to document the outcome(s)? Yes, though Bridges and Solomon (2016) suggest that sufficient detail was not provided regarding data processing and presenting the results.	**2**

Short citation (Author, year, or ID)	DOWCO09C		
Full citation (or link)	Dow Corning Corporation. 2009. Trophic dilution of cyclic volatile methylsiloxane (cVMS) materials in a temperate freshwater lake. HES study no: 10771-108. May 18.		
Study type (e.g., OECD Guideline if applicable)	N		
Study Director (if applicable)	Powell, D.E. and K.B. Woodburn (Authors)		
GLP Compliance (if applicable)	N		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	aquatic food web. The TMF for D4 was 0.3. BSAFs for D4 ranged from 0.8 to 19.2, but reflect an analytical bias and should be used with caution.		
Statistical method and kinetic calculations	The LOO, MDL, and LOQ were determined as a function of the variance associated with replicate analyses of matrix-free blanks (LOD and replicate analyses of samples containing a small, but measurable amount of cVMS materials (MDL, LOQ). Single-factor analysis of variance (ANOVA) was performed to test for differences in mean masses and concentrations (wet weight basis) of cVMS materials measured in reagent blanks, field blanks, and reference samples associated with each analytical batch of field samples (surface sediments, benthic macroinvertebrates, and fish). Two-factor ANOVA (without replication) was performed to test for differences across shore-to-shore transects and across upstream-to downstream locations for concentrations of cVMS materials (dry weight, wet weight, and TOG-normalized), TOC, 15N, and 13C measured in surface sediments. If the omnibus *F* value indicated significant differences between the mean values, a Tukey HSD multiple comparisons test (for equal sample sizes) or a Tukey-Kramer multiple comparisons test (for unequal sample sizes) was used to compare individual means. All cVMS concentration data was converted to lipid weight for regression analyses and for calculation of trophic magnification factors (TMFs). The Pearson product-moment correlation coefficient (r) was used to evaluate correlations between variables in surface sediments.	Were statistics and/or kinetic calculations described and consistent? Yes	**1**

Short citation (Author, year, or ID)	**DOWCO09C**		
Full citation (or link)	**Dow Corning Corporation. 2009. Trophic dilution of cyclic volatile methylsiloxane (cVMS) materials in a temperate freshwater lake. HES study no: 10771-108. May 18.**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**Powell, D.E. and K.B. Woodburn (Authors)**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	The Pearson product-moment correlation coefficient (r) was also used to evaluate correlations between cVMS materials (D4, D5, and D6) and lipid content of benthic macroinvertebrates and fish. Log transformation of concentration data was used to generate normally distributed data for regression and correlation analyses.		
Plausibility of results	Quality control method implemented to reduce cVMS contamination by cleaning all lab ware and equipment. All quality control methods were clearly documented, and numerous laboratory blanks, replicates, reference samples, internal standards, were explained. However, no mention of quality control relating to use of personal care products and eliminating use prior and during sample collection and experiments.	Were the study results reasonable? Yes, though more detail was needed on =methods used to avoid contamination by study personnel.	**2**
		Score (18–72); without two criteria, possible score was 16–62:	**29**

Short citation (Author, year, or ID)	**DOWCO10A**		
Full citation (or link)	**Dow Corning Corporation. 2010. Preliminary Assessment of Cyclic Volatile Methylsiloxane (cVMS) Materials in Surface Sediments, Cores, Zooplankton, and Fish of Lake Opeongo, Ontario, Canada. HES study no.: 10806-108.**		
Study type (e.g., OECD Guideline if applicable)	**Preliminary assessment of cVMS (D4, D5, and D6) concentrations, fish, zooplankton, sediment**		
Study Director (if applicable)	**Powell, D.A. (author)**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, and D6	Was the test substance identified definitively? No. samples were from the field, and cVMS's used as internal standards were not thoroughly documented.	**3**
Composition (purity, origin); single substance (not mixture)	Source: Dow for reference materials, unknown for field samples Purity: unknown Unknown if reference material was blend of D4-D6, or for a single substance.	Was the source and purity identified? No. samples were from the field, and cVMS's used in reference materials were not thoroughly documented.	**3**
Preparation	cVMS concentrations were determined from field samples and not prepared in the lab. Surface sediment samples were collected in October 2007. Surface sediments were collected from 7 locations in the lake using a box core. Sediment cores were collected from 2 locations using a box core. Bulk zooplankton was collected using a plankton tow from 8 locations. Fish samples were collected with a gill net. Lake trout were stored individually in polyethylene bags whereas forage fish were pooled and stored as composite samples (n=50) by species. Amount of sampling locations was not provided in the text. Samples collected in the field were immediately placed in food storage bags (sediment) and stored in a cooler. Samples were processed at the lab within 4-6 hours of collection. Samples underwent extraction prior to quantitative analyses. Standard reference materials were not available; for this study reference materials were prepared by Dow for sediment and fish matrices.	Was the test substance preparation described and appropriate for the test system? Substance preparation did not occur; handling and storage of cVMS is more applicable and was found to be mostly appropriate. However, standard reference materials were not available and had to be prepared by Dow. To avoid contamination, a thorough QC program was developed. However, this did not include controlling use of personal care products by personnel.	**2**
Test Design			

Short citation (Author, year, or ID)	**DOWCO10A**		
Full citation (or link)	**Dow Corning Corporation. 2010. Preliminary Assessment of Cyclic Volatile Methylsiloxane (cVMS) Materials in Surface Sediments, Cores, Zooplankton, and Fish of Lake Opeongo, Ontario, Canada. HES study no.: 10806-108.**		
Study type (e.g., OECD Guideline if applicable)	**Preliminary assessment of cVMS (D4, D5, and D6) concentrations, fish, zooplankton, sediment**		
Study Director (if applicable)	**Powell, D.A. (author)**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test system (suitability)	Field collection of various biological samples at Lake Opeongo, followed by lab analysis.	Was the test method appropriate for the test substance? Lake Opeongo is the largest lake in Ontario, Canada and represents a freshwater food web. The lake as a history of limited human disturbance and is free from cVMS materials originating from sewage and runoff.	**1**
Test conditions (monitored and appropriate)	Data included sediment and biological samples from Lake Opeongo, Canada. Samples were analyzed for cVMS.	Were test conditions appropriate? This is a field study, so the conditions were appropriate. Lake Opeongo has been previous studies and characterized. Published work is available for the lake.	**1**
Consistency (across groups)	Sample size was consistent between yellow perch and lake trout, though no mention of sample size for lake trout.	Were test conditions consistent across groups? Sample sizes overall appear consistent. Table 5 provided information on the total number of fish samples analyzed for cVMS – these sample sizes are consistent among the three species.	**1**
Test organisms (if applicable)	Species: Yellow perch *(Perea flavescens) n = 50;* Cisco *(Coreogonus artedi) n = 50;* Lake trout *(Salvelinus namaycush) n= unknown;* Zooplankton Age: determined using scales, only for lake trout Physical measurements: fresh weight, total length Stable isotope analysis: removed muscle Health/Handling: No health observations provided. Acclimation was not relevant to the study.	Was the inoculum or test organism appropriate? Yes, however missing sample size collected for lake trout.	**2**
Controls	Field quality control samples for sediment and zooplankton. Matrix-free blanks, background correction, reagent blanks, replicates, field spikes, reference samples, and use of internal standards	Were the appropriate controls used? Mentions that QC program for fish was not sufficient to evaluate sample contamination that may have occurred during collection, handling, shipment, storage, and processing therefore fish QC samples not collected in field. Field personnel told to not use personal care products during field collection.	**1**
Duration	Not relevant to study.	Was the duration of the study appropriate? Characterization of cVMS in environment was from one time point only, not designed as a long-term monitoring study.	**-**
Methods and Observations			

Short citation (Author, year, or ID)	**DOWCO10A**		
Full citation (or link)	**Dow Corning Corporation. 2010. Preliminary Assessment of Cyclic Volatile Methylsiloxane (cVMS) Materials in Surface Sediments, Cores, Zooplankton, and Fish of Lake Opeongo, Ontario, Canada. HES study no.: 10806-108.**		
Study type (e.g., OECD Guideline if applicable)	**Preliminary assessment of cVMS (D4, D5, and D6) concentrations, fish, zooplankton, sediment**		
Study Director (if applicable)	**Powell, D.A. (author)**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Observations (half-lives, coefficients, etc.)	Characterization of lake (sediment) and biological samples was reported. Sediment samples were analyzed for total carbon, total inorganic carbon, total organic carbon, total water content, and total organic matter content. Fish were analyzed for water content, lipid content, and isotopic nitrogen and carbon signatures. Zooplankton were characterized for cVMS. BMF was calculated.	Were the appropriate outcomes reported? Methodology was appropriate to report outcomes of interest. More fish samples/fish QA should have been better considered before proceeding with study.	**2**
Control performance	Highly variable reagent blank data and made quantification of cVMS materials difficult in all matrices. This represented a systematic contamination issues that was not resolved.	Was control performance acceptable? Multiple controls used as QA measures however, the study had contamination issues that made the data unrealizable.	**3**
Sampling adequacy (frequency, duration)	Samples were collected in October 2007. Field sampling occurred during 1 period.	Was the timing and frequency of sampling adequate? No, only one sampling event was conducted.	**3**
Analytical method and measurements of test substance to verify presence in test system	Data included sediment characterization (carbon coulometry analysis, loss-on-ignition analysis), fish characterization (water and lipid content, stable isotope analysis), cVMS analysis using GC-MS (extraction from sediments, fish, zooplankton) Isotope analysis for biological samples (except zooplankton) for whole body lipid content and whole body concentrations of D4, D5, and D6.	Were appropriate methods of analysis used? Details provided on origin of reference materials for sediment and fish references.	**1**
Results			
Confounding variables	Decontamination performed as best as possible for all equipment in direct contact with sediment samples. If equipment could not be decontaminated, it was discarded. Air contamination in field avoided by processing samples downwind of lake and upwind of buildings/other cVMS sources. Cross contamination of sediment core tubes by using tubes only once and using decontamination steps for other equipment.	What sources of variability were noted and did they affect the outcome assessment? ANOVA tests were used to compare cVMS materials measures in reagent blanks, field blanks, and reference samples associated with each batch of field samples (sediment, zooplankton, fish). Tukey HSD test was used to compare individual; means, specific confounding variables not mentioned.	**3**

Short citation (Author, year, or ID)	**DOWCO10A**		
Full citation (or link)	**Dow Corning Corporation. 2010. Preliminary Assessment of Cyclic Volatile Methylsiloxane (cVMS) Materials in Surface Sediments, Cores, Zooplankton, and Fish of Lake Opeongo, Ontario, Canada. HES study no.: 10806-108.**		
Study type (e.g., OECD Guideline if applicable)	**Preliminary assessment of cVMS (D4, D5, and D6) concentrations, fish, zooplankton, sediment**		
Study Director (if applicable)	**Powell, D.A. (author)**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Outcomes unrelated to exposure	Determined that biological variability had greatest impact on BMF.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)? Health data not recorded for fish. Unrelated conditions were not accounted for.	**3**
Data	Data reported in comparison to various endpoints (LOD, MDL). High background contamination and low concentrations in the biological samples made the data statistically the same as the reagent blanks. <u>Results summary:</u> Analytical method detection limits expressed on the basis of wet weight across all matrices (sediment, zooplankton, and fish) ranged from 0.47 to 0.90 ng/g ww for D4, from 1.79 to 3.10 ng/g ww for D5, and from 0.15 to 0.74 ng/g ww for D6. Mean predator-prey specific biomagnification factors (BMF) ranged from 1.9 to 2.4 for D4, from 2.3 to 5.2 for D5, and from 1.4 to 1.5 for D6.	Were the data appropriately reported to document the outcome(s)? No, contamination in reagent blanks made data unreliable.	**3**
Statistical method and kinetic calculations	Used documented detection levels, limit of detection, method detection level, limit of quantification, below detection; ANOVA, Tukey HSD, predatory-prey biomagnification calculations	Were statistics and/or kinetic calculations described and consistent? Yes. Provided details on why all measurements were necessary and how stats were used/selected.	**1**
Plausibility of results	All controls documented, however the low levels of D4, D5, and D6 that were detected in fish likely originated from personal care products used during recreational activities that were presumably rinsed off the body directly into the water column of the lake.	Were the study results reasonable? Yes, study estimates that cVMS concentrations are likely low in the environment, but data are not reliable and only provides an estimate.	**3**
		Score (18–72); without one criterion, possible range of score was 17-68:	**36**

Short citation (Author, year, or ID)	DOWCO10B		
Full citation (or link)	Dow Corning Corporation. 2010. Bioaccumulation and trophic transfer of cyclic volatile methylsiloxane (cVMS) materials in the aquatic marine food webs of the inner and outer Oslofjord, Norway. HES Study No.: 11060-108.		
Study type (e.g., OECD Guideline if applicable)	N		
Study Director (if applicable)	Powell, D.E. (Author)		
GLP Compliance (if applicable)	N		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, and D6	Was the test substance identified definitively? No, samples were from the field. Reference sediment was spiked with D4, D5, and D6. No details on use of cVMS in reference biological samples.	**3**
Composition (purity, origin); single substance (not mixture)	Source: unknown Origin: unknown Purity: unknown	Was the source and purity identified? No	**3**
Preparation	No details on preparation of D4, D5, and D6. Collected samples prepared in the field before transport to the laboratory. Samples distributed between Dow and Evonik. Sediments and fish stored as individual samples, macroinvertebrates and zooplankton stored as composite samples per species. Surface sediment collected as duplicate sediment cores from four locations in inner Oslofjord and three location in outer Oslofjord. Six vertical hauls were made for zooplankton in the inner Oslofjord and three hauls in the outer Oslofjord, from single locations. Samples were composited. The same method was followed for macroinvertebrates but amount of sample locations or replicates collected was not provided. Collected fish using bottom trawl were separated by species and placed into plastic storage bags. Field quality control samples consisted of skin-off fillets. The control was divided into three and placed into three different types of storage containers as the field blank, net-blank (in mesh bag and placed at throat of trawl before deployment), and the	Was the test substance preparation described and appropriate for the test system? Yes. However, substance preparation did not occur; handling and storage of samples for cVMS analysis is more applicable. To check for sample contamination, air quality analysis occurred during sampling and indicated contamination in field samples from air likely not significant. Analysis of CQ samples (field blanks, net blanks, and process blanks) indicated samples were not contaminated during trawling or on-board processing. No mention of methods used to reduce contamination in the field or lab from personnel. No details on methods used to reduce volatilization. Dow and Evonik laboratories divided all samples and processed without prior standardization or validation between the two labs. Field sample storage also varied for all samples.	**3**

Short citation (Author, year, or ID)	DOWCO10B		
Full citation (or link)	**Dow Corning Corporation. 2010. Bioaccumulation and trophic transfer of cyclic volatile methylsiloxane (cVMS) materials in the aquatic marine food webs of the inner and outer Oslofjord, Norway. HES Study No.: 11060-108.**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**Powell, D.E. (Author)**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	process blank (left on processing table as other samples were processed). Sample storage was dependent upon the final destination (Dow or Evonik) but included glass containers. No field quality control samples were collected for sediment, zooplankton, and macroinvertebrates.		
Test Design			
Test system (suitability)	Field collection Oslofjord, Norway, in marine environment, followed by lab analysis. Samples collected in 2008. Surface sediment, zooplankton, benthic macroinvertebrates, shellfish, and finfish collected using gravity core, vertical zooplankton haul, benthic sled, and bottom trawl.	Was the test method appropriate for the test substance? Yes, the field location represents a well-studied marine environment with a marine food web, and therefore is appropriate for the study.	**1**
Test conditions (monitored and appropriate)	Data included representative samples of fish, shellfish, zooplankton, sediment, and macroinvertebrates. Biological samples analyzed for stable isotope fractionation using 13C-carbon and 15N- nitrogen, water content, lipid content, and whole body concentrations of siloxanes. Biological samples processed as whole body homogenates of individual or pooled samples. Sediment samples analyzed for total organic carbon, total inorganic carbon, total carbon, total water content, total organic matter content, and siloxane concentrations.	Were test conditions appropriate? Previous published literature has described the Oslofjord, with extensive monitoring occurring since the 1970s, though much of the work has not been published internationally. Yes, sampling was done with care for siloxane contamination. Methods seemed appropriate but the siloxane method used in this study has not been validated.	**2**
Consistency (across groups)	Inconsistent in comparable sample sizes between species. Biological samples were collected in both the inner and outer Oslofjord – the same sample sizes were not collected for the same species.	Were test conditions consistent across groups? No, sample sizes were not consistent between similar species, and were not consisted within the same species for the two sampling locations (inner and outer Oslofjord). No, use of two laboratories without harmonizing methods caused inconsistency is results.	**3**

Short citation (Author, year, or ID)	**DOWCO10B**		
Full citation (or link)	**Dow Corning Corporation. 2010. Bioaccumulation and trophic transfer of cyclic volatile methylsiloxane (cVMS) materials in the aquatic marine food webs of the inner and outer Oslofjord, Norway. HES Study No.: 11060-108.**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**Powell, D.E. (Author)**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test organisms (if applicable)	Multiple biological species collected. Below, sample size is listed first for the inner, than outer, Oslofjord. No scientific name for the species was provided unless otherwise noted. Worm (n=1, 2) Sea urchin (n=0, 4) Mussel (species A) (n=2, 3) Mussel (species B) (n=2, 3) Blue mussel (*Mytilus edulis*) (n=5, 0) Net plankton (n=2,1) Jellyfish (n=2, 1) Northern shrimp (*Pandalus borealis*) (n=6, 6) Atlantic herring (*Clupea harengus*) (n=6, 0) Atlantic cod (*Gadus morhua*) (n=6, 7) Coalfish (*Pollachius virens*) (n=6, 6) European whiting (*Merlangius merlangus*) (n=6, 0) Haddock (*Melanogrammus aeglefinus*) (n=4, 12) North Atlantic Pollock (*Pollachius pollachius*) (n=6, 0) Norway pout (*Trisopterus esmarkii*) (n=6, 10) Poor cod (*Trisopterus minutus*) (n=6, 0) European hake (*Merluccius merluccius*) (n=4, 0) European plaice (*Pleuronectes platessa*) (n=6, 5) Long rough dab (*Hippoglossoides pltaessoides*) (n=6, 6) Starry skate (*Amblyraja radiate*) (n=0, 6) Common sole (*Solea vulgaris*) (n=0, 6) Vahls' eelpout (*Lycodes vahlii*) (n=6, 0)	Was the inoculum or test organism appropriate? Yes, organisms represented various components of the food web. However, sample sizes were not even between species, or between sampling locations for the same species.	**2**
Controls	Air samples collected in parallel with aquatic samples to check for potential contamination. Field QC samples collected for bottom trawl samples. Field quality control samples consisted of skin-off fillets for Atlantic cod from outer Oslofjord. Field crew did not use personal care products during collection. Standard reference materials for D4, D5, or D6 not available in any matrix and may account for inter-laboratory bias or precision errors. Background	Were the appropriate controls used? Yes, though different methods between the two laboratories made use of all controls less reliable.	**3**

Short citation (Author, year, or ID)	DOWCO10B		
Full citation (or link)	**Dow Corning Corporation. 2010. Bioaccumulation and trophic transfer of cyclic volatile methylsiloxane (cVMS) materials in the aquatic marine food webs of the inner and outer Oslofjord, Norway. HES Study No.: 11060-108.**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**Powell, D.E. (Author)**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	corrections made for cVMS materials in samples using reagent blanks. Use of detection limits, reagent blanks, field blanks, laboratory blanks, field replicates, laboratory replicates, extract replicates, field spikes, laboratory spikes, reference samples, and internal standards.		
Duration	Not relevant to this study. Sampling was a one-time event rather than a time series monitoring study.	Was the duration of the study appropriate? Characterization of cVMS in environment was from one time point only, not designed as a long-term monitoring study.	**-**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Carbon flow, relative trophic levels of consumers in the food web	Were the appropriate outcomes reported? Yes	**1**
Control performance	Control performance was documented, though less reliable given two laboratories analyzed the data without a standard methodology or use of standards.	Was control performance acceptable? No, given controls and analyses were not standardized.	**3**
Sampling adequacy (frequency, duration)	Field sampling occurred during 1 period. Samples were collected in October 2008.	Was the timing and frequency of sampling adequate? No, only one sampling event was conducted.	**2**
Analytical method and measurements of test substance to verify presence in test system	Biological samples analyzed for stable isotope fractionation using 13C-caron and15N- nitrogen, water content, lipid content, and whole body concentrations of siloxanes. Biological samples processed as whole body homogenates of individual or pooled samples. Sediment samples analyzed for total organic carbon, total inorganic carbon, total carbon, total water content, total organic matter content, and siloxane concentrations. cVMS was measured with gas chromatography-mass spectrometry (GC-MS).	Were appropriate methods of analysis used? Yes, however lack of standardization and common methodologies between the two laboratories made comparison of data less reliable.	**2**
Results			
Confounding variables	Detection levels between laboratories were not standardized and not comparable.	What sources of variability were noted and did they affect the outcome assessment? Yes, variability did affect the outcome. Due to	**3**

Short citation (Author, year, or ID)	DOWCO10B		
Full citation (or link)	**Dow Corning Corporation. 2010. Bioaccumulation and trophic transfer of cyclic volatile methylsiloxane (cVMS) materials in the aquatic marine food webs of the inner and outer Oslofjord, Norway. HES Study No.: 11060-108.**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**Powell, D.E. (Author)**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
		merging of the Dow and Evonik datasets, TMFs and BMFs were much more variable.	
Outcomes unrelated to exposure	Data with negative values was excluded from the dataset and treated as a missing value.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)? Yes	**2**
Data	Yes, raw data tables were provided. Results summary: Carbon flow found to be benthic in origin. Food web length was 2.6 trophic steps in inner Oslofjord and 2.4 trophic steps in outer Oslofjord TMF < 1.0 for D4, D5, and D6. (range 0.2 to 0.6) Predator-prey specific biomagnification factor (BMF) 0.7-1.8	Were the data appropriately reported to document the outcome(s)? Yes, but raw data were only partially provided.	**2**
Statistical method and kinetic calculations	Detection levels. Statistical analysis compared between the Dow and Evonik datasets. Type I error used to judge significance all of statistical tests. Outliers identified and removed under defined conditions. cVMS concentrations normalized to lipid content to calculate BMF and TMF. Log transformation of concentration data used to generate normally distributed data for regression analysis. Additional statistical analyses were performed, and are not described here.	Were statistics and/or kinetic calculations described and consistent? Yes	**1**
Plausibility of results	Air quality analysis indicated contamination if field samples from air likely not significant. Analysis of CQ samples (field blanks, net blanks, and process blanks) indicated samples were not contaminated during trawling or on-board processing. Due to merging of the Dow and Evonik datasets, TMFs and BMFs were much more variable.	Were the study results reasonable? Moderately reasonable. The field collection and study design was appropriate. The use of two laboratories was not appropriate given that the laboratories did not standardize methodologies or use similar standards. However, there is confidence that the conclusion that no relevant biomagnification is accurate.	**2**
		Score (18–72); without one criterion, possible score was 17–66:	**38**

Short citation (Author, year, or ID)	**HONG14A**		
Full citation (or link)	**Hong, W-J., H. Jia, C. Liu, Z. Zhang, Y. Sun, and Y-F. Li. 2014. Distribution, source, fate and bioaccumulation of methyl siloxanes in marine environment. Environmental Pollution 191:175-181.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, D6, D7, and linear siloxanes (L4-L17). A surrogate standard, Tetrakis (trimethylsiloxy)-silane was also used.	Was the test substance identified definitively? No, samples were from the field. However, compounds mentioned were used as reference materials, not as the test substances. PCB-30 was used as an internal standard.	**1**
Composition (purity, origin); single substance (not mixture)	Purchased from Tokyo Chemical Industry (Wellesley Hills, MA, USA). Only D7 was purchased from Sigma-Aldrich. No details on purity was provided. Tetrakis (trimethylsiloxy)-silane has a purity of 97% and was purchased from Sigma-Aldrich.	Was the source and purity identified? Only source was provided.	**2**
Preparation	Surface seawater samples collected at 29 sites in the marine environment in and around Dalian, China in July 2011. Sites were divided into three categories: urban, semi-urban, and non-urban. Six bottom fish samples were collected in an urban sampling location. Sediment samples were collected from 20 sites. Surface sediment was collected with bucket grabs. Seawater and sediment samples were composites of 5 sub-samples collected at each sampling location. Effluent from five municipal sewage treatment plants were collected. All samples were collected and stored in solvent rinsed glass bottles with Teflon lined caps. Samples stored in refrigerator and/or mixed with dichloromethane until further extraction and analysis. Fish samples were further prepared for individual organ and muscle samples. A total of six samples for gills,	Was the test substance preparation described and appropriate for the test system? Yes, siloxanes were purchased and used as calibration/quality control steps. Methods were also used to avoid contamination of samples during collection, storing, and preparation prior to lab analysis.	**1**

Short citation (Author, year, or ID)	**HONG14A**		
Full citation (or link)	**Hong, W-J., H. Jia, C. Liu, Z. Zhang, Y. Sun, and Y-F. Li. 2014. Distribution, source, fate and bioaccumulation of methyl siloxanes in marine environment. Environmental Pollution 191:175-181.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	muscles, intestines, and body were prepared. One sample for brains, eyes, and sexual glands was prepared.		
Test Design			
Test system (suitability)	Field collection near Dalian, China in the marine environment in 2011-2012, followed by lab analysis.	Was the test method appropriate for the test substance? Yes, field location is in the northern Chinese Sea and represents appropriate location for sampling the marine food web. Additionally, siloxane production in China is growing and therefore sample locations represent realistic exposure scenario.	**1**
Test conditions (monitored and appropriate)	Data included representative samples of fish, sediment, seawater, and effluent from the Chinese Sea near urban, semi-urban, and non-urban environments. Fish samples were analyzed individually for various muscle and organ components. Samples were analyzed for siloxane content, lipid content when applicable, and total organic matter when applicable.	Were test conditions appropriate? This is a field study, so test conditions were appropriate. This is a coastal marine area in China, though there is no mention or previous work/characterization of the environment.	**2**
Consistency (across groups)	Only one organism used to assess bioaccumulation.	Were test conditions consistent across groups? Similar sample sizes were analyzed for whole body, muscle, gill, and intestine (n=6), but fish samples were divided differently for the eyes, brain, and sexual glands (n=1). Overall, the sample size for one fish species collected (n=6) was low. 29 sediment samples were collected, and these samples were divided into three categories (near urban environment, middle distance from urban environment, far from urban environment). No details are provided on the number of sediment samples in each category.	**3**
Test organisms (if applicable)	Fish collected were described as bottom feeders (*Hexagrammos otakii*). Only one fish species used; food web was not assessed.	Was the inoculum or test organism appropriate? No, unknown if sample comparisons are relevant given unknown species identification and differences that may be related to different life histories. Ages were also not factored into the fish samples.	**3**
Controls	Spiked samples with surrogate standard and internal standards were used. During sampling in the field, field and trip blanks were performed for every fifth water sample. Calibration curves, limits of detection, method	Were the appropriate controls used? Yes, the study used an appropriate amount of blanks and controls. However, these methods and controls are not standardized, nor have they been validated.	**2**

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Full citation (or link)	**Hong, W-J., H. Jia, C. Liu, Z. Zhang, Y. Sun, and Y-F. Li. 2014. Distribution, source, fate and bioaccumulation of methyl siloxanes in marine environment. Environmental Pollution 191:175-181.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	detection limits, and instrument detection limits were determined.		
Duration	Not relevant to this study. Sampling was a one-time event rather than a time series monitoring study.	Was the duration of the study appropriate? Characterization of cVMS in environment was from one time point only, not designed as a long-term monitoring study.	**-**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Environmental siloxane concentrations were determined, as well as bioaccumulation factor (BAF) and biota-sediment accumulation factor (BSAF) calculated.	Were the appropriate outcomes reported? Yes	**1**
Control performance	All compounds were identified within ±0.05 min of the calibration standard and the selected mass ions. The recoveries of surrogate standard (M4Q) were 82% - 108% from all samples.	Was control performance acceptable? Yes, not noted otherwise. Multiple controls used as QA measures.	**1**
Sampling adequacy (frequency, duration)	Surface seawater samples collected at 29 sites in the marine environment in and around Dalian, China in July 2011. Sites were divided into three categories: urban, semi-urban, and non-urban. Six bottom fish samples were collected in an urban sampling location. Sediment samples were collected from 20 sites. Surface sediment was collected with bucket grabs. Seawater and sediment samples were composites of 5 sub-samples collected at each sampling location. Effluent from five municipal sewage treatment plants were collected. All samples were collected and stored in solvent rinsed glass bottles with Teflon lined caps. Samples stored in refrigerator and/or mixed with dichloromethane until further extraction and analysis.	Was the timing and frequency of sampling adequate? Yes, adequate samples were collected for sediment and seawater but a greater sample size for fish samples would have been appropriate. Supplemental information contains maps of sampling locations. However, only one sampling event was conducted.	**3**

Short citation (Author, year, or ID)	**HONG14A**		
Full citation (or link)	**Hong, W-J., H. Jia, C. Liu, Z. Zhang, Y. Sun, and Y-F. Li. 2014. Distribution, source, fate and bioaccumulation of methyl siloxanes in marine environment. Environmental Pollution 191:175-181.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	Fish samples were further prepared for individual organ and muscle samples. A total of six samples for gills, muscles, intestines, and body were prepared. One sample for brains, eyes, and sexual glands was prepared.		
Analytical method and measurements of test substance to verify presence in test system		Were appropriate methods of analysis used? Yes, though methods not validated.	**2**
Results			
Confounding variables	Contamination and volatilization are an important confounding factors	What sources of variability were noted and did they affect the outcome assessment? Several measures were taken to prevent contamination during sampling. Samples were taken back to the laboratory for further processing. No mention about avoiding volatilization.	**2**
Outcomes unrelated to exposure	None mentioned.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)? Not applicable	**-**
Data	Raw data tables are provided in the supplemental information. mean concentrations of total methyl siloxanes were 46.1 ± 27.2 ng/L in seawater 12.4 ± 5.39 ng/g dry weight (dw) in sediment 5.10 ± 1.34 wet weight (ww) in fish mean value of biota-sediment accumulation factor (BSAF) was 0.716 ± 0.456 for D4, 0.103 ± 0.0771 for D5, 1.06 ± 0.528 for D6 and 0.877± 0.530 for D7	Were the data appropriately reported to document the outcome(s)? Yes, however raw data would be more appropriate. Supplemental information contains following data: composition percentage of cVMSs found in seawater, sediment, and fish body (not raw data), instrument contamination tests results (raw data), field blank, transport blank, and procedure blank data (raw data), blank samples for biota and sediment (raw data), detection limits (raw data), recoveries for cVMSs from spiked samples in seawater, sediment and biota (raw data), and parameters used for calculating BSAF.	**2**
Statistical method and kinetic calculations	Below detection limit calculation described. Bioaccumulation factor (BAF) and biota-sediment accumulation factor (BSAF) calculated.	Were statistics and/or kinetic calculations described and consistent? No, more details needed for the analyses used.	**3**
Plausibility of results	Ranges of concentrations found in the environment and similar to those measured in other work. Steps taken to prevent siloxane contamination of samples from other sources such as personal care products. Field and trip blanks used. Numerous quality control steps described.	Were the study results reasonable? Yes, controls used well that provides plausibility to results. However, the methods were not validated.	**2**

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Full citation (or link)	**Hong, W-J., H. Jia, C. Liu, Z. Zhang, Y. Sun, and Y-F. Li. 2014. Distribution, source, fate and bioaccumulation of methyl siloxanes in marine environment. Environmental Pollution 191:175-181.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
		Score (18–72); without two criteria, possible score was 16–64:	**31**

Short citation (Author, year, or ID)	**JIA15A**		
Full citation (or link)	**Jia, H., Z. Zhang, C. Wang, W-J. Hong, Y. Sun, and Y-F. Li. 2015. Trophic transfer of methyl siloxanes in the marine food web from coastal area of Northern China. Environmental Science & Technology 49(5):2833-2840.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, D6, and D7	Was the test substance identified definitively? No samples were from the field. Yes Quantification of cVMS was based on external calibration standards.	**1**
Composition (purity, origin); single substance (not mixture)	D4, D5, and D6 were obtained from Tokyo Chemical Industry (Wellesley Hills, MA). D7 and linear siloxanes (L4 ~L17) was obtained from Sigma-Aldrich (St. Louis, MO).	Was the source and purity identified? Source was identified but purity was not.	**2**
Preparation	Purchased siloxanes were used for standard samples. Little detail available on methods for these samples. Fish were collected by bottom trawl. Mollusk samples were collected from a culturing raft site. Clamworm and Neptunes were collected using a bucket. Biological organisms (fish and crustacean) collected using a bottom trawl collected at site S2. Mussels collected from a culturing raft as sites S2 and S3. Clamworm and arthritic Neptune collected from sediment using a bucket at sites S1, S2, and S3. Sea lettuce collected form seawater at sites S1, S2, and S3. All samples were collected in September 2013. All samples were packed in glass vials and frozen immediately in the field. All samples were prepared out doors and personal care products were prohibited 24h before sampling. No mention of a clean room for sample analysis. Information not provided in the main text on sampling locations and amount of biological organisms caught at each site. Length, weight, moisture content, fat content,	Was the test substance preparation described and appropriate for the test system? No test substance was prepared. Samples were collected from the field, therefore, sampling and handling is more appropriate to evaluate here. Details were provided on methods used to prevent sample contamination.	**3**

Short citation (Author, year, or ID)	**JIA15A**		
Full citation (or link)	**Jia, H., Z. Zhang, C. Wang, W-J. Hong, Y. Sun, and Y-F. Li. 2015. Trophic transfer of methyl siloxanes in the marine food web from coastal area of Northern China. Environmental Science & Technology 49(5):2833-2840.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	and isotope analysis, recorded for all biological samples in the supplemental information.		
Test Design			
Test system (suitability)	Field collection near Dalian Bay, on the Chinese Yellow Sea in September 2013.	Was the test method appropriate for the test substance? Yes, field location is in the northern Chinese Sea and represents appropriate location for sampling the marine food web. Additionally, siloxane production in China is growing and therefore sample locations represent realistic exposure scenario.	**1**
Test conditions (monitored and appropriate)	Data included biological samples from three sample locations (S1, S2, and S3) near Dalian Bay, on the Chinese Yellow Sea. Samples were analyzed for cVMS.	Were test conditions appropriate? This is a field study, so test conditions were appropriate. The sampling location (Dalian Bay) seems appropriate as representing biological diversity, but no details are provided if the location has been previously studies or characterized.	**2**
Consistency (across groups)	Biota sample sizes ranged from 3 to 26.	Were test conditions consistent across groups? No, similar sample sizes for biological species were not collected.	**3**
Test organisms (if applicable)	Fish: pacific herring (*Clupea pallasii*) n = 26, mackerel (*Pneumatophorus japonicus*) n = 15, greenling (*Hexagrammos otakii*) n = 7, schlegel's black rockfish (*Sebastes schlegelii*) n = 6, sea catfish (*Synechogobius hasta*) n = 7. Crustacean: mud crab (*Scylla serrata*) n =5. Mollusks: mactra quadrangularis (*Mactra veneriformis*) n = 7, short-necked clam (*Ruditapes philippinarum*) n = 10 mussel (*Mytilus galloprovincialis*) n = 10, black fovea snail (*Omphalus rustica*) n = 3, arthritic Neptune (*Neptunea cumingi*) n = 3. Clamworm: (*Perinereis aibuhitensis*) n = 6.	Was the inoculum or test organism appropriate? Yes, numerous species representing multiple levels in the food web were collected.	**1**

Short citation (Author, year, or ID)	**JIA15A**		
Full citation (or link)	**Jia, H., Z. Zhang, C. Wang, W-J. Hong, Y. Sun, and Y-F. Li. 2015. Trophic transfer of methyl siloxanes in the marine food web from coastal area of Northern China. Environmental Science & Technology 49(5):2833-2840.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	Other: Sea lettuce (*Ulva pertusa*) n= 8. Additional biological details such as moisture content, fat content, body length, and body weight are presented in the SI.		
Controls	One blank field sample collected every 10 biota samples. Instrument contamination was performed. Sample treatments were performed in air cabinets. All samples spiked with labeled recovery standard. Also used procedural blanks to check for contamination. Methods recovery were assessed with spiked samples. Organic solvent and reagent blanks used.	Were the appropriate controls used? Yes, the study used an appropriate amount of blanks and controls. However, these methods and controls are not standardized, nor have they been validated.	**2**
Duration	Not relevant to this study. Sampling was a one-time event rather than a time series monitoring study.	Was the duration of the study appropriate? Characterization of cVMS in environment was from one time point only, not designed as a long-term monitoring study.	**--**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Environmental siloxane concentrations, trophic magnification factor, lipid normalization, and relative trophic level were all determined.	Were the appropriate outcomes reported? Yes	**1**
Control performance	Use of benchmark chemical (BDE-99). Sample preparation occurred outdoors to reduce risk of contamination. All personal care products were prohibited from use 24 hours in advance of sample collection. All personnel wore gloves. All equipment, utensils were cleaned in acetone prior to use.	Was control performance acceptable? Yes, the study used an appropriate amount of blanks and controls. However, these methods and controls are not standardized, nor have they been validated.	**2**
Sampling adequacy (frequency, duration)	Field sampling occurred during 1 period in September 2013.	Was the timing and frequency of sampling adequate? No, only one sampling event was conducted.	**3**
Analytical method and measurements of test substance to verify presence in test system	Acetone rinsed bistoury method used to collect biological samples if collection portion only. Some biological samples were whole body. All samples packed in solvent rinsed glass with Teflon lined caps. All samples frozen immediately after collection.	Were appropriate methods of analysis used? Yes	**1**

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Full citation (or link)	**Jia, H., Z. Zhang, C. Wang, W-J. Hong, Y. Sun, and Y-F. Li. 2015. Trophic transfer of methyl siloxanes in the marine food web from coastal area of Northern China. Environmental Science & Technology 49(5):2833-2840.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	Biological samples were homogenized, underwent extraction, and quantified with GC-MS. External calibration standards used. Samples for polybrominated diphenyl ethers analysis were extracted and analyzed according to the methods established at the National Laboratory for Environmental Texting (NLET), Environment Canada, and have been reported previously. Details for PBDEs analysis were in the SI. Samples for lipid analysis underwent extraction and then determined gravimetrically. Stable isotope ratios of carbon and nitrogen were measured with an isotope mass spectrometer and an elemental analyzer.		
Results			
Confounding variables	Contamination and volatilization are an important confounding factors.	What sources of variability were noted and did they affect the outcome assessment? Several measures were taken to prevent contamination during sampling. Samples were taken back to the laboratory for further processing. No mention of using a clean room. No mention about avoiding volatilization.	**2**
Outcomes unrelated to exposure	Uncertainty associated with lipid normalization for sea lettuce based use of normalization based on biota assumptions, not land plant assumptions.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)? Yes, variability in calculations was noted but likely did not affect outcome.	**1**
Data	Raw data tables were provided for cVMS concentration data in the supplemental information. The trophic magnification factor (TMF) for	Were the data appropriately reported to document the outcome(s)? Yes, however raw data would be more appropriate. More data was presented in the supplemental information file, the SI was reviewed and included TMF values ad relationship to log Kow, biological sample details, content of cVMSs in blanks, limit of detection, limit of	**2**

Short citation (Author, year, or ID)	**JIA15A**		
Full citation (or link)	**Jia, H., Z. Zhang, C. Wang, W-J. Hong, Y. Sun, and Y-F. Li. 2015. Trophic transfer of methyl siloxanes in the marine food web from coastal area of Northern China. Environmental Science & Technology 49(5):2833-2840.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	D4 = 1.16 D5 = 1.77 D6 = 1.01 D7 = 0.85 Study collected multiple species from different levels in the food web to determine trophic magnification factors. The authors reported on a zooplankton-invertebrate-fish aquatic food web and TMF was not statistically significant for D_4 (correlation coefficient or $R^2 = 0.02$, $p = 0.16$). These aquatic data indicate that neither trophic magnification nor trophic dilution was occurring with D4 in this aquatic food web.	quantification, cVMS concentrations from all biological samples (raw data), and input variables for the Monte Carlo simulation.	
Statistical method and kinetic calculations	Trophic magnification factor, lipid normalization, limit of detection, limit of quantification, and relative trophic level were all determined. Monte Carlo simulations also performed in R.	Were statistics and/or kinetic calculations described and consistent? Yes	**1**
Plausibility of results	Steps taken to prevent siloxane contamination of samples from other sources such as personal care products. Field and trip blanks used. Numerous quality control steps described.	Were the study results reasonable? Yes, controls used well that provides plausibility to results. However, the methods were not validated.	**2**
		Score (18–72); without one criterion, possible score was 17–66:	**30**

Short citation (Author, year, or ID)	**KIERK11A**		
Full citation (or link)	**Kierkegaard A, von Egmond R, McLachlan ME. 2011. Cyclic Volatile Methylsiloxane Bioaccumulation in Flounder and Ragworm in the Humber Estuary. Environmental Science & Technology 45:5936−5942.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for bioaccumulation**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, and D6	Was the test substance identified definitively? No, samples were from the field. However, procedural blank and internal matrix control (herring homogenate) were used to verify cVMS concentrations.	**2**
Composition (purity, origin); single substance (not mixture)	Source: Not applicable; this is a field study Purity: Not applicable; this is a field study Single substance: Not applicable; this is a field study	Was the source and purity identified? No, samples were from the field. However, procedural blank and internal matrix control (herring homogenate) were used to verify cVMS concentrations.	**2**
Preparation	cVMS concentrations were determined from field samples and not prepared in the lab. Fish samples were wrapped in aluminum foil and stored in polyethylene (PE) bags to transfer to laboratory, where muscle samples were removed in a clean-air fume hood, wrapped in foil and vacuum-sealed PE pouches, and frozen until analysis. Ragworm samples were collected in plastic buckets with estuary water and a thin layer of sediment and transferred to the lab, where they were allowed to depurate for 24 hrs. Ragworm samples were then wrapped in aluminum foil and sealed in PE bags and frozen until analysis. Sediments were collected from 1-2 cm depth within 1 m of the ragworm collection sites, placed in jars and stored until analysis. Field blanks were used to check for air contamination in the field and lab while processing the samples. No details on study personnel avoidance of personal care products prior or during sampling were provided.	Was the test substance preparation described and appropriate for the test system? Substance preparation did not occur; handling and storage of samples for cVMS analysis is more applicable. While a clean-air fume hood was used to prepare fish samples and several blanks and a control sample were used, no details on study personnel avoidance of personal care products prior or during sampling were provided.	**3**
Test Design			
Test system (suitability)	Field collection of benthic organisms and sediment at 6 intertidal sites in Humber Estuary, England in September-October 2009, followed by lab analysis.	Was the test method appropriate for the test substance? Humber Estuary drains approximately 20% of England's surface area in a heavily populated area; thus, this area seems appropriate for analysis.	**1**
Test conditions (monitored and appropriate)	Data included sediment, whole samples of ragworm (*Hediste diversicolor*) and muscle samples of flounder	Were test conditions appropriate? This is a field study, so test conditions were appropriate. Collecting sediment, ragworms and	**2**

Short citation (Author, year, or ID)	**KIERK11A**		
Full citation (or link)	**Kierkegaard A, von Egmond R, McLachlan ME. 2011. Cyclic Volatile Methylsiloxane Bioaccumulation in Flounder and Ragworm in the Humber Estuary. Environmental Science & Technology 45:5936−5942.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for bioaccumulation**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	(*Pleuronectes flesus*) from six intertidal stations in Humber Estuary, England. Samples were analyzed for cVMS, and select PCB congeners for comparison to cVMS. Sediments were also analyzed for organic carbon content.	flounder is appropriate to evaluate bioaccumulation. However, there was no mention of other studies or monitoring at this location.	
Consistency (across groups)	Laboratory testing conditions by use of various QA methods created consistency.	Were test conditions consistent across groups? Yes, the same six locations were sampled for each media type, but sample size was slightly different between ragworm (n=19) and flounder (n=27).	**2**
Test organisms (if applicable)	Species: Ragworm (*Hediste diversicolor*), n=19. Flounder (*Pleuronectes flesus*), n=27. Age: not determined. Physical measurements: fresh weight, total length. cVMS: whole samples of ragworms; muscle of fish. Health/Handling: No health observations provided. Acclimation was not relevant to the study.	Was the inoculum or test organism appropriate? Yes, the species used were appropriate. However, sample size seemed small for the large size of the estuarine system. In addition, only muscle of the fish, not whole-body samples were analyzed for cVMS concentrations.	**3**
Controls	Field blanks, procedural blanks, internal matrix control (herring homogenate). cVMS results were not blank corrected.	Were the appropriate controls used? Samples were prepared both outdoors and in the lab, but blanks were used to monitor air contamination. However, these methods and controls are not standardized, nor have they been validated.	**3**
Duration	Not relevant to study.	Was the duration of the study appropriate? Characterization of cVMS in the environment was from one time point only, not designed as a long-term monitoring study.	**-**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Concentrations of cVMS in sediment, ragworm, and flounder samples, and bioaccumulation of cVMS in ragworms and flounder relative to PCB180. Actual bioaccumulation factors were not reported. Lipid concentrations or water concentrations of cVMS were not measured.	Were the appropriate outcomes reported? Methodology was appropriate to report outcomes of interest. More samples should have been considered before proceeding with study. D4 bioaccumulation was compared to PCB180, as a reference compound. However, it was not demonstrated that the sediments under investigation had similar levels of D4 and PCB180. PCB180 is a legacy compound that was used as a reference compound and is expected to be distributed	**3**

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Full citation (or link)	**Kierkegaard A, von Egmond R, McLachlan ME. 2011. Cyclic Volatile Methylsiloxane Bioaccumulation in Flounder and Ragworm in the Humber Estuary. Environmental Science & Technology 45:5936−5942.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for bioaccumulation**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
		evenly in these sediments, but D4 is still being used in industry and would likely show a gradient from an anthropogenic source.	
Control performance	Control herring homogenates could not be used to estimate repeatability in this study (while it could be for D5 and D6) because the D4 concentrations in the control herring homogenates were below the limit of quantification. The differences in the field blanks and sediment and ragworm samples were low. However, the D4 contents of the field blanks and unexposed pouches were similar, showing low contamination during ragworm processing.	Was control performance acceptable? Yes, while multiple controls were used as QA measures (field blank and matrix interference), the matrix interference results were below the limit of quantification, and the all of the sediment results and several biota samples results were similar to the field blanks for D4.	**3**
Sampling adequacy (frequency, duration)	Field sampling occurred during 1 period. Only six stations were sampled during one sampling period.	Was the timing and frequency of sampling adequate? No, only one sampling event was conducted.	**3**
Analytical method and measurements of test substance to verify presence in test system	cVMS were analyzed by a purge and trap method developed by this group followed by gas chromatography/mass spectrometry (GC/MS). The purge and trap method was later refined by Borgå et al. (2013) because it appeared to be less reliable than other methods. Borgå K, Fjeld E, Kierkegaard A, McLachlan ME. 2013. Consistency in Trophic Magnification Factors of Cyclic Methyl Siloxanes in Pelagic Freshwater Food Webs Leading to Brown Trout. Environmental Science & Technology 47:14394−14402.	Were appropriate methods of analysis used? Details were provided on origin of reference materials for field blanks and internal matrix (herring homogenate). The cVMS extraction method was less reliable than other methods. In addition, D4 results for many samples were below the limit of quantification.	**3**
Results			
Confounding variables	Contamination and volatilization are important confounding factors for D4 studies.	What sources of variability were noted and did they affect the outcome assessment? It is not stated how measures were taken to prevent contamination during sampling; however field blanks were taken during sampling and processing. Samples were processed in the open air and D4 is very volatile.	**3**
Outcomes unrelated to exposure	None mentioned.	Not applicable.	**-**

Short citation (Author, year, or ID)	**KIERK11A**		
Full citation (or link)	**Kierkegaard A, von Egmond R, McLachlan ME. 2011. Cyclic Volatile Methylsiloxane Bioaccumulation in Flounder and Ragworm in the Humber Estuary. Environmental Science & Technology 45:5936−5942.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for bioaccumulation**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Data	cVMS data were reported on a dry weight basis for sediment and wet weight basis for biota in the SI. <u>Results Summary:</u> All sediment concentrations of D4 were below the limit of quantification. Ragworm D4 concentrations ranged from <1.6 to 20 ng/g wet weight (11 of 19 samples were below the limit of quantification). Flounder D4 concentrations ranged from <0.8 to 10.4 ng/g wet weight (25 of 34 samples were below the limit of quantification). D4 bioaccumulation was estimated by comparing log B_{ratio} values, which are calculated using the concentrations in the organisms and sediment from the same sites and comparing those values to B_{ratio} values for PCB180. This study found that D4 bioaccumulates to a greater extent than PCB180. The mean B_{ratio} of D4 was 6 in ragworms and 14 in flounder, 4-5x higher than for D5.	Were the data appropriately reported to document the outcome(s)? No, the B_{ratio} values do not provide BAF or BSAF data for D4. While this concluded that D4 bioaccumulates to a greater extent than PCB180, much of the concentrations were below the limit of quantification, which results in a great degree of uncertainty. In addition, the study did not show that the sediments contained similar concentrations of D4 and the reference compound (PCB180).	**4**
Statistical method and kinetic calculations	No discussion of statistical or kinetic calculations were made.	Were statistics and/or kinetic calculations described and consistent? No. Also, BAFs were not calculated in a way that is useful beyond other studies that use PCB180 as a reference compound.	**4**
Plausibility of results	All controls well-documented, but concentrations of D4 were below the limit of quantification in many samples leads to uncertainty with the reported data.	Were the study results reasonable? Yes, controls provided plausibility to results. BAFs were not calculated in a way that is useful beyond other studies that use PCB180 as a reference compound. However, this purge and trap extraction method was later refined by Borgå et al. (2013) because it appeared to be less reliable than other methods. Also, concentrations of D4 were below the limit of quantification in many samples, which leads to uncertainty with the reported data. Statistical analyses were not used for assessing the data.	**2**
		Score (18–72); without 2 criteria, possible score was 16–64:	**43**

Short citation (Author, year, or ID)	**KIERK13A**		
Full citation (or link)	**Kierkegaard A, Bignert A, McLachlan ME. 2013. Cyclic volatile methylsiloxanes in fish from the Baltic Sea. Chemosphere 93:774−778.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for biomagnification**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, and D6	Was the test substance identified definitively? No, samples were from the field. However, procedural blank and internal matrix control (herring homogenate) were used to verify cVMS concentrations.	**2**
Composition (purity, origin); single substance (not mixture)	Source: Not applicable; this is a field study Purity: Not applicable; this is a field study Single substance: Not applicable; this is a field study	Was the source and purity identified? No, samples were from the field. However, procedural blank and internal matrix control (herring homogenate) were used to verify cVMS concentrations.	**2**
Preparation	cVMS concentrations were determined from field samples and not prepared in the lab. Fish (herring) samples were wrapped in aluminum foil and stored in polyethylene (PE) bags to transfer to laboratory, where muscle samples were removed under a room with counter-flow of particle filtered air, wrapped in foil and vacuum-sealed PE pouches and frozen until analysis. Grey seal blubber was obtained from 2 seals that drowned in nets in the autumn of 2008. Field blanks were used to check for air contamination in the field while collecting some of the fish samples. No details on study personnel avoidance of personal care products prior or during sampling were provided.	Was the test substance preparation described and appropriate for the test system? Substance preparation did not occur; handling and storage of samples for cVMS analysis is more applicable. While a room with counter-flow of particle filtered air was used to prepare fish samples, and several blanks and a control sample were used, no details on study personnel avoidance of personal care products prior or during sampling were provided.	**3**
Test Design			
Test system (suitability)	Field collection of fish from 12 sites in the Baltic Sea mostly in 2007 (1 station in 2008 and another station in 2010) and blubber from 3 drowned seals from nets north of Vastervik, Sweden in 2008, followed by lab analysis.	Was the test method appropriate for the test substance? The Baltic Sea is proximal to a large human population and is susceptible to contamination.	**1**
Test conditions (monitored and appropriate)	Data included sediment, muscle samples of herring (*Clupea harengus*) from 10 stations in the Baltic Sea, Sweden, and blubber samples from three drowned grey seals (opportunistic samples). Samples were analyzed for cVMS and lipid content.	Were test conditions appropriate? This is a field study, so test conditions were appropriate. Collecting herring and seal blubber is appropriate to evaluate biomagnification. Herring are the primary (82%) dietary item of grey seals.	**1**

Short citation (Author, year, or ID)	**KIERK13A**		
Full citation (or link)	**Kierkegaard A, Bignert A, McLachlan ME. 2013. Cyclic volatile methylsiloxanes in fish from the Baltic Sea. Chemosphere 93:774−778.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for biomagnification**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Consistency (across groups)	3 herring samples were analyzed for cVMS from 10 stations, although 12 stations were sampled. 3 seal blubber samples were analyzed for cVMS from 1 station.	Were test conditions consistent across groups? No, several more fish samples were collected than seal blubber samples.	**3**
Test organisms (if applicable)	Species: Herring (*Clupea harengus*), 3 samples from each station. Grey seal (*Halichoerus grypus*), 3 individual samples from one station. Age: determined. Physical measurements: weight and body length of fish and seal. cVMS: muscle of herring, blubber of seals. Health/Handling: No health observations provided. Acclimation was not relevant to the study.	Was the inoculum or test organism appropriate? Yes, the species used were appropriate. However, sample size seemed small for the seals. In addition, only muscle of the fish, not whole-body samples were analyzed for cVMS concentrations.	**3**
Controls	Field blanks, procedural blanks, internal matrix control (herring homogenate). cVMS results were not blank corrected.	Were the appropriate controls used? Samples were prepared both outdoors and in the lab, but blanks were used to monitored air contamination. However, these methods and controls are not standardized, nor have they been validated.	**3**
Duration	Not relevant to study.	Was the duration of the study appropriate? Characterization of cVMS in the environment was from one time point only, not designed as a long-term monitoring study.	**-**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Concentrations of cVMS in herring and seal blubber samples, and biomagnification potential of cVMS in seals was reported.	Were the appropriate outcomes reported? Methodology was appropriate to report outcomes of interest. Only three samples were available for seals, which is small but not unexpected. Trophic magnification factors (TMF), a measure of biomagnification, was not reported. However, comparison of fish concentrations and blubber concentrations were made to assess the biomagnification of D4.	**3**
Control performance	Control herring homogenates could not be used to estimate repeatability in this study (while it could be for D5 and D6) because the D4 concentrations in the control herring homogenates were below the limit of quantification. The differences in the field blanks and	Was control performance acceptable? No, the herring homogenates (matrix interference sample) could not be used for D4 because the concentrations were below the limit of quantification. The average recoveries for the samples in this study was 82% for D4. Extraction efficiency was 53% for D4 and thought to be an overestimate. D4 was	**3**

Short citation (Author, year, or ID)	KIERK13A		
Full citation (or link)	Kierkegaard A, Bignert A, McLachlan ME. 2013. Cyclic volatile methylsiloxanes in fish from the Baltic Sea. Chemosphere 93:774−778.		
Study type (e.g., OECD Guideline if applicable)	No guideline. Field study for biomagnification		
Study Director (if applicable)	N/A		
GLP Compliance (if applicable)	No		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	biota samples were low. However, the D4 contents of the field blanks and unexposed pouches were similar, showing low contamination during processing.	present in quantifiable amounts in 33% of the samples. Several fish results were similar to the field blanks for D4.	
Sampling adequacy (frequency, duration)	Field sampling occurred during mostly 1 period; a second set of fish samples were collected on a separate event but it was limited. 12 stations were sampled for fish (cVMS data provided only for 10 stations), but only one location for seal samples.	Was the timing and frequency of sampling adequate? No, sampling mostly was just conducted over 1 period. While a second collection of fish was made it was to help interpret the seal blubber results; it was not a full repeat of the first sampling round.	**3**
Analytical method and measurements of test substance to verify presence in test system	cVMS were analyzed by a purge and trap method developed by this group followed by gas chromatography/mass spectrometry (GC/MS). The purge and trap method was later refined by Borgå et al. (2013) because it appeared to be less reliable than other methods. Borgå K, Fjeld E, Kierkegaard A, McLachlan ME. 2013. Consistency in Trophic Magnification Factors of Cyclic Methyl Siloxanes in Pelagic Freshwater Food Webs Leading to Brown Trout. Environmental Science & Technology 47:14394−14402.	Were appropriate methods of analysis used? Details were provided on origin of reference materials for field blanks and internal matrix (herring homogenate). Methods seemed appropriate but the cVMS extraction method used in this study was later refined by Borgå et al. (2013) because it appeared to be less reliable than other methods. In addition, D4 results for 67% of the fish samples were below the limit of quantification.	**3**
Results			
Confounding variables	Contamination and volatilization are important confounding factors for D4 studies.	What sources of variability were noted and did they affect the outcome assessment? It is not stated how measures were taken to prevent contamination during sampling; however, field blanks were taken during sampling and processing and samples were processed in a room with a room with counter-flow of particle filtered air.	**3**
Outcomes unrelated to exposure	None mentioned.	Not applicable.	**-**
Data	cVMS data for herring were reported on a lipid weight basis. All other data were reported in the SI. <u>Results Summary:</u> Herring muscle contained approximately 10 ng/g lipid weight. Concentrations of D4 in herring were on average	Were the data appropriately reported to document the outcome(s)? Yes, the data were presented appropriately. D4 concentrations in herring were 4x lower than those in seal blubber. However, the herring samples were collected the year before the seal blubber samples were collected. In addition, the three seal blubber samples	**3**

Short citation (Author, year, or ID)	**KIERK13A**		
Full citation (or link)	**Kierkegaard A, Bignert A, McLachlan ME. 2013. Cyclic volatile methylsiloxanes in fish from the Baltic Sea. Chemosphere 93:774−778.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for biomagnification**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	5x lower than those of D6 and 18x lower than those of D5. To assess biomagnification of cVMS, the lipid-normalized concentrations in herring were compared with the concentrations in seal blubber, but D4 concentrations in herring sampled in the same years as the seals were below the limit of quantification. The median concentration of D4 in herring from a nearby station (Byxelkrok) the previous year was 4x higher than the median concentration in seal blubber suggesting that D4 did not biomagnify in grey seals.	contained D4 below the limits of quantification. Lack of data on whole body concentrations is a significant weakness	
Statistical method and kinetic calculations	No kinetic calculations were made but fish cVMS concentrations were compared using either Bartlett's test or Mann-Whitney U-test.	Were statistics and/or kinetic calculations described and consistent? Yes, provided details on why all measurements were necessary and how stats were used/selected.	**2**
Plausibility of results	All controls well-documented, but concentrations of D4 were below the limit of quantification in many samples, which leads to uncertainty with the reported data.	Were the study results reasonable? Yes, controls provided plausibility to results. However, this purge and trap extraction method was later refined by Borgå et al. (2013) because it appeared to be less reliable than other methods. Also, concentrations of D4 were below the limit of quantification in many samples, which leads to uncertainty with the reported data.	**2**
		Score (18–72); without 2 criteria, possible score was 16–64:	**39**

Short citation (Author, year, or ID)	**KROGS14A**		
Full citation (or link)	**Krogseth IS, Warner NA, Christensen GN, Whelan MJ, Breivik K, Evenset A, Wasbotten IH. 2014. Understanding the fate and bioaccumulation of cyclic volatile methyl siloxanes Arctic lakes. Organohalogen Compounds 76:186−189.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for bioaccumulation, biomagnification/trophic magnification/modeling**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, and D6	Was the test substance identified definitively? No, samples were from the field. No additional information was provided.	**4**
Composition (purity, origin); single substance (not mixture)	Source: Not applicable; this is a field study Purity: Not applicable; this is a field study Single substance: Not applicable; this is a field study	Was the source and purity identified? No, samples were from the field. No additional information was provided.	**4**
Preparation	cVMS concentrations were determined from field samples. Precautionary steps were taken to minimize background contamination of cVMS in the samples, and field blanks were included for all matrices, but information was provided. Instead, the paper cited another paper (Warner NA, Kozerski G, Durham J, Koerner M, Gerhards R, Campbell R, McNett DA. 2013. Chemosphere 93(5):749-756).	Was the test substance preparation described and appropriate for the test system? Substance preparation did not occur, but handling and storage of samples for cVMS analysis is more applicable given the concerns for contamination. However, very little information of the samples handling and storage were provided. The paper did not that several steps were taken to minimize background contamination.	**3**
Test Design			
Test system (suitability)	Field collection of representatives of the food web at Lake Storvannet in Hammerfest in northern Norway in March/April 2014, followed by lab analysis.	Was the test method appropriate for the test substance? Lake Storvannet is well-characterized and receives sewage from leaking pipes and overflow events.	**1**
Test conditions (monitored and appropriate)	Data included sediment, water and representatives of the food web in this lake. Samples of surface water, sediment, zooplankton, benthic fauna, sticklebacks (fish), stationary trout (brown trout), and char were analyzed for stable isotopes, cVMS, and lipid content.	Were test conditions appropriate? This is a field study, so test conditions were appropriate. The food web had been characterized.	**1**
Consistency (across groups)	No information on sample size was provided.	Were test conditions consistent across groups? No information was provided.	**4**
Test organisms (if applicable)	Species: Zooplankton, benthic fauna, sticklebacks, stationary or brown trout, char. No samples sizes were provided. Age: not stated. Physical measurements: not stated.	Was the inoculum or test organism appropriate? Yes, these seem to be appropriate organisms. No further information was provided.	**3**

Short citation (Author, year, or ID)	**KROGS14A**		
Full citation (or link)	**Krogseth IS, Warner NA, Christensen GN, Whelan MJ, Breivik K, Evenset A, Wasbotten IH. 2014. Understanding the fate and bioaccumulation of cyclic volatile methyl siloxanes Arctic lakes. Organohalogen Compounds 76:186−189.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for bioaccumulation, biomagnification/trophic magnification/modeling**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	cVMS and Stable isotope analysis: zooplankton, benthic fauna, fish. Health/Handling: No health observations provided. Acclimation was not relevant to the study.		
Controls	Field blanks were included for all matrices, but no further information on controls was described.	Were the appropriate controls used? No information was provided.	**4**
Duration	Not relevant to study.	Was the duration of the study appropriate? Characterization of cVMS in environment was from one time point only, not designed as a long-term monitoring study.	**-**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	No information was provided.	Were the appropriate outcomes reported? No information or data was provided in this report since it was just a preliminary discussion of the study.	**4**
Control performance	No information was provided.	Was control performance acceptable? No, while multiple controls used as QA measures (field blank and matrix interference), some of the results of the field blanks for D4 were very close to the results for the biota samples from the field.	**3**
Sampling adequacy (frequency, duration)	Field sampling occurred during 1 season, but was planned for another season.	Was the timing and frequency of sampling adequate? Only first season of sampling had been conducted in March/April 2014. This seemed appropriate but more sampling was planned.	**3**
Analytical method and measurements of test substance to verify presence in test system	The water and sewage samples were analyzed for cVMS using an existing static headspace method coupled to gas chromatography with mass spectrometric detection (GC-MS).sSediment and biota samples were extracted using a modified version of previously established liquid extraction methods, followed by analysis on GC-MS. Additional parameters such as organic carbon content in water and sediments, lipid content in biota, and stable isotopes (15N and 13C) in sediment and biota were determined. Precautionary steps were taken to minimize background contamination of cVMS in the	Were appropriate methods of analysis used? Methods seemed appropriate, but the cVMS method used in this study has not been validated.	**3**

Short citation (Author, year, or ID)	KROGS14A		
Full citation (or link)	Krogseth IS, Warner NA, Christensen GN, Whelan MJ, Breivik K, Evenset A, Wasbotten IH. 2014. Understanding the fate and bioaccumulation of cyclic volatile methyl siloxanes Arctic lakes. Organohalogen Compounds 76:186−189.		
Study type (e.g., OECD Guideline if applicable)	No guideline. Field study for bioaccumulation, biomagnification/trophic magnification/modeling		
Study Director (if applicable)	N/A		
GLP Compliance (if applicable)	No		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	samples, and field blanks were included for all matrices.		
Results			
Confounding variables	Contamination and volatilization are important confounding factors for D4 studies.	What sources of variability were noted and did they affect the outcome assessment? Precautionary steps were taken to minimize background contamination of cVMS in the samples, and field blanks were included for all matrices, but information was provided. Instead, the paper cited another paper (Warner NA, Kozerski G, Durham J, Koerner M, Gerhards R, Campbell R, McNett DA. 2013. Chemosphere 93(5):749-756).	**2**
Outcomes unrelated to exposure	None mentioned.	Not applicable.	**-**
Data	Only modeled cVMS concentrations were presented in this preliminary study report.	Were the data appropriately reported to document the outcome(s)? No, too little information was provided.	**4**
Statistical method and kinetic calculations	These data were collected to develop a model to predict fate and bioaccumulation of cVMS in Arctic lakes.	Were statistics and/or kinetic calculations described and consistent? Provided details on why all measurements were necessary and how stats were used/selected. No detailed information was provided.	**-**
Plausibility of results	Results were predicted concentrations of cVMS in media but were preliminary results.	Were the study results reasonable? Yes, but results were only preliminary and did not provide bioaccumulation factors.	**4**
		Score (18–72); without 3 criteria, possible score was 15–60:	**47**

Short citation (Author, year, or ID)	**KROGS17A**		
Full citation (or link)	**Krogseth IS, Undeman E, Evenset A, Christensen GN, Whelan MJ, Breivik K, Warner NA. 2017. Elucidating the behavior of cyclic volatile methylsiloxanes in a subarctic freshwater food web: a modeled and measured approach. Environmental Science & Technology 51:12489−12497.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for bioaccumulation, biomagnification/trophic magnification/modeling**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, and D6	Was the test substance identified definitively? No, samples were from the field. However, radiolabeled surrogate standards and internal matrix control (cod) was used to verify cVMS concentrations.	**2**
Composition (purity, origin); single substance (not mixture)	Source: Not applicable; this is a field study Purity: Not applicable; this is a field study Single substance: Not applicable; this is a field study	Was the source and purity identified? No, samples were from the field. However, radiolabeled surrogate standards and internal matrix control (cod) was used to verify cVMS concentrations.	**2**
Preparation	cVMS concentrations were determined from field samples and not prepared in the lab. Fish were caught using traps, nets, lines and hooks. Benthic fauna were collected by hauling 500 µm trawl along the bottom. All samples were wrapped in aluminum foil, placed in zip lock bags, and transported in chilled boxes to the lab where they were stored frozen until sample preparation. In the lab, fish samples were prepared with metal utensils on glass surfaces. Personnel avoided using personal care products during field and lab work. Radiolabeled surrogate standards were used, and internal matrix control (cod) was used to verify cVMS concentrations.	Was the test substance preparation described and appropriate for the test system? Substance preparation did not occur, but handling and storage of samples for cVMS analysis is more applicable and that was appropriate given the concerns for contamination. Field and lab personnel were told to not use personal care products during sampling and analysis.	**2**
Test Design			
Test system (suitability)	Field collection of representatives of the food web at Lake Storvannet in Hammerfest in northern Norway in March, May and June 2014, followed by lab analysis.	Was the test method appropriate for the test substance? Lake Storvannet receives sewage from leaking pipes and overflow events. Lake Storvannet was chosen as (i) the lake and its food web is relatively well-studied, (ii) measurements of PCBs from lake water, sediments, and biota are available for model evaluation purposes, and (iii) a study of cVMS behavior in the physical environment of the lake has already been carried out.	**1**
Test conditions (monitored and appropriate)	Data for representatives of the food web in this lake. Samples of benthic fauna, sticklebacks (fish), stationary trout, and char were analyzed for stable isotopes, cVMS, and lipid content. Data from a companion study (Krogseth	Were test conditions appropriate? This is a field study, so test conditions are not appropriate. The lake has been well studied.	**1**

Short citation (Author, year, or ID)	KROGS17A		
Full citation (or link)	Krogseth IS, Undeman E, Evenset A, Christensen GN, Whelan MJ, Breivik K, Warner NA. 2017. Elucidating the behavior of cyclic volatile methylsiloxanes in a subarctic freshwater food web: a modeled and measured approach. Environmental Science & Technology 51:12489−12497.		
Study type (e.g., OECD Guideline if applicable)	No guideline. Field study for bioaccumulation, biomagnification/trophic magnification/modeling		
Study Director (if applicable)	N/A		
GLP Compliance (if applicable)	No		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	et al. 2017. Understanding of cyclic volatile methyl siloxane fate in a high latitude lake is constrained by uncertainty in organic carbon−water partitioning. Environ. Sci. Technol. 51:401−409) and other studies were used to characterize the lake.		
Consistency (across groups)	11 char samples, 13 trout samples, 5 stickleback samples, 2 *Chironomidae* composite samples, and 2 *Pisidium* sp. composite samples were collected.	Were test conditions consistent across groups? Dissimilar sample sizes of biota from the food web were collected.	**3**
Test organisms (if applicable)	Species: Benthic fauna (2 pooled samples of *Chironomidae* and 2 pooled samples of *Pisidium* sp.); 5 pooled samples of three-spined sticklebacks (*Gasterosteus aculeatus*), 13 individual brown or stationary trout (*Salmo trutta*) 11 individual char (*Salvelinus alpinus*). Age: provided for trout and char Physical measurements: Body weight and length of char and trout, liver weight of char and trout, stomach contents of char and trout, body weight of sticklebacks. cVMS, lipid content (fish only), and stable isotope analysis: benthic fauna, fish. Health/Handling: No health observations provided. Acclimation was not relevant to the study.	Was the inoculum or test organism appropriate? Yes, this food web had been previously characterized and monitored for several years. However, sample size seemed small for the large size of the lake system. In addition, only muscle and livers of char and trout, not whole-body samples were analyzed for cVMS concentrations.	**3**
Controls	Field blanks, dissection blanks, and reference blanks, radio-labeled surrogates for cVMS, procedural blanks, and reference blank tissues. cVMS results were not blank corrected.	Were the appropriate controls used? Yes, several QA samples were collected along the process. However, these methods and controls are not standardized, nor have they been validated.	**2**
Duration	Not relevant to study.	Was the duration of the study appropriate? Characterization of cVMS in environment was from one year only, not designed as a long-term monitoring study.	**-**
Methods and Observations			

Short citation (Author, year, or ID)	**KROGS17A**		
Full citation (or link)	**Krogseth IS, Undeman E, Evenset A, Christensen GN, Whelan MJ, Breivik K, Warner NA. 2017. Elucidating the behavior of cyclic volatile methylsiloxanes in a subarctic freshwater food web: a modeled and measured approach. Environmental Science & Technology 51:12489−12497.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for bioaccumulation, biomagnification/trophic magnification/modeling**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Observations (half-lives, coefficients, etc.)	Concentrations of cVMS on a wet weight and lipid normalized basis, and stable isotopes 13C, 15N, 34S. Benthic organisms were not depurated prior to chemical analysis and could have contained sediment particles.	Were the appropriate outcomes reported? Methodology was appropriate to report outcomes of interest. More samples for the benthic organisms should have been collected and analyzed in this study. Benthic organisms were not depurated prior to analysis, so data should be used with some caution.	**2**
Control performance	The dissection blanks for the muscle tissue did not display significantly higher concentrations than the reference muscle material for any of the cVMS. Average recoveries for D4 in tissues was approximately 80%.	Was control performance acceptable? Yes, multiple controls used as QA measures (field blanks), and results for *Chironomidae, Pisidium*, and stickleback samples were all above the limit of quantification and field blanks.	**2**
Sampling adequacy (frequency, duration)	Field sampling occurred during 1 year. 2-13 samples of biota were collected per species.	Was the timing and frequency of sampling adequate? No, only one year was studied, and few samples were collected for the bottom of the food web (2 samples for benthic fauna), this seems low given the size of the lake system and the possible variability in D4 concentrations in field samples.	**3**
Analytical method and measurements of test substance to verify presence in test system	All samples were extracted for cVMS using a biphasic cold solvent extraction, based on a previously published method for sediments (Krogseth et al. 2017. Understanding of cyclic volatile methyl siloxane fate in a high latitude lake is constrained by uncertainty in organic carbon−water partitioning. Environ. Sci. Technol. 51:401−409), but was adapted to biotic tissues. Analysis of cVMS was carried out on an Agilent 7890A GC connected to an Agilent 5975C MS detector and a Gerstel MPS3 autosampler. Precautionary steps were taken to minimize background contamination of cVMS in the samples, and field blanks were included for all matrices. Isotope ratios of 13C, 15N, and 34S in muscle tissue (char and trout) or whole-body homogenates (stickleback, chironomid larvae, Pisidium sp.) were determined at The Institute for Energy Technology (Kjeller, Norway) using a Eurovector EA3028 element analyzer for combustion and a 2 m Poraplot Q GC column and a Horizon isotope Ratio Mass Spectrometer from Nu-instruments for analysis of N_2, CO_2, and SO_2.	Were appropriate methods of analysis used? Methods seemed appropriate, but the cVMS method used in this study has not been validated.	**2**
Results			

Short citation (Author, year, or ID)	**KROGS17A**		
Full citation (or link)	**Krogseth IS, Undeman E, Evenset A, Christensen GN, Whelan MJ, Breivik K, Warner NA. 2017. Elucidating the behavior of cyclic volatile methylsiloxanes in a subarctic freshwater food web: a modeled and measured approach. Environmental Science & Technology 51:12489−12497.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for bioaccumulation, biomagnification/trophic magnification/modeling**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Confounding variables	Contamination and volatilization are important confounding factors for D4 studies.	What sources of variability were noted and did they affect the outcome assessment? Several measures were taken to prevent contamination during sampling. The dissection blanks for the muscle tissue did not display significantly higher concentrations than the reference muscle material for any of the cVMS. No methods were used to address volatilization of D4.	**2**
Outcomes unrelated to exposure	None mentioned.	Not applicable.	**-**
Data	cVMS and stable isotope data are available. Results Summary: Average concentrations of D4 in whole *Pisidium, Chironomidae,* and sticklebacks were 4.7, 9.9, and 13 ng/g wet weight, respectively. Muscle concentrations of D4 in Arctic char ranged from less than the Limit of quantification to 19 ng/g wet weight; muscle concentrations of D4 in brown trout were all below the limit of quantification. These data suggest that D4 does not exhibit trophic biomagnification. D4 BSAFs for char was ≤6.2. D4 was nondetect in trout, so no BSAF was calculated. D4 BSAF for sticklebacks was 1.5 (0.5-3.3).	Were the data appropriately reported to document the outcome(s)? Yes.	**1**
Statistical method and kinetic calculations	These data were collected to develop a model to predict fate and bioaccumulation of cVMS in subarctic lakes. A new bentho-pelagic version of the ACC-HUMAN model was evaluated for polychlorinated biphenyls (PCBs) and applied to cVMS in combination with measurements to explore their bioaccumulation behavior in a subarctic lake. Predictions agreed better with measured PCB concentrations in Arctic char (*Salvelinus alpinus*) and brown trout (*Salmo trutta*) when the benthic link was included than in the pelagic-only model. Concentrations were lower for D4 and D6 than for D5, and none of the cVMS displayed trophic magnification. Predicted cVMS concentrations were lower than measured	Were statistics and/or kinetic calculations described and consistent? Provided details on why all measurements were necessary and how stats were used/selected. These statistics and kinetic calculations used in the model seemed appropriate, but benthos concentrations were underpredicted by the model.	**3**

Short citation (Author, year, or ID)	**KROGS17A**		
Full citation (or link)	**Krogseth IS, Undeman E, Evenset A, Christensen GN, Whelan MJ, Breivik K, Warner NA. 2017. Elucidating the behavior of cyclic volatile methylsiloxanes in a subarctic freshwater food web: a modeled and measured approach. Environmental Science & Technology 51:12489−12497.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Field study for bioaccumulation, biomagnification/trophic magnification/modeling**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	in benthos, but agreed well with measurements in fish. cVMS removal through fecal egestion, biotransformation and ventilation are important predicted loss mechanisms for all fish, but ventilation is also particularly important for the benthic-feeding fish. Predictions were highly sensitive to the partition coefficient between organic carbon and water (K_{OC}) and its temperature dependence, as this controlled bioavailability for benthos (the main source of cVMS for fish).		
Plausibility of results	All controls well-documented, but benthic samples were not depurated so some sediment particles may have been present, thus influencing the benthic concentrations.	Were the study results reasonable? Yes, controls provided plausibility to results. However, the methods were not validated and benthic samples were not depurated, which leads to uncertainty with the reported data.	**2**
		Score (18–72); without 2 criteria, possible score was 16–64:	**33**

Short citation (Author, year, or ID)	**MCGOL14A**		
Full citation (or link)	**McGoldrick, D.J., C. Chan, K.G. Drouillard, M.J. Keir, M.G. Clark, and S.M. Backus. 2014. Concentrations and trophic magnification of cyclic siloxanes in aquatic biota from the Western Basin of Lake Erie, Canada. Environmental Pollution 186:141-148.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	cVMS compounds were not described. Additionally, no details provided on preparation of the isotopically enriched 13C-D4, 13C-D5, and 13C-D6, used as internal standards.	Was the test substance identified definitively? No, cVMSs compounds were not described as samples were from the field. Rather, the isotopic internal standards were described.	**2**
Composition (purity, origin); single substance (not mixture)	No information provided. Source: Not applicable; this is a field study Purity: Not applicable; this is a field study Single substance: Not applicable; this is a field study	Was the source and purity identified? D4, D5, and D6 labeled with 13C, though no details on where purchased from or any physical chemical properties was provided. Supplemental information presents details on the determination of 13C-labeled surrogates.	**2**
Preparation	Biological samples were collected in summer/fall 2009 as part of a routine monitoring program through Environment Canada. All samples were collected in the western basin of Lake Erie and walleye fish samples were obtained from Ontario Ministry of Natural Resources. Methods were used to avoid contamination of fish samples by avoiding contact with skin and ship surfaces. Forage fish were collected using bottom trawl. Zookplankton was collected using horizontal tows of a conical plankton net. Benthic invertebrates were collected using a modified epibenthic sled. All biota samples were immediately frozen and transported to the laboratory for long-term storage until homogenization. Walleye and drum were homogenized. All other fish were divided in groups based on length to create five sub-samples. The fish processing lab is under positive pressure and physically separate from the main work area. Air entering the space is filtered and access is restricted to a single employee. Homogenized biota spiked with 13C-labeled siloxanes and used to calculate relative siloxane concentrations in biota.	Was the test substance preparation described and appropriate for the test system? Test substance was not prepared. Field samples were collected, thus sampling and handling is more appropriate to assess here. Methods used to avoid contamination in the field and in the lab.	**2**
Test Design			
Test system (suitability)	Aquatic biota collected in the western basin of Lake Erie near Middle Sister Island in summer and fall 2009, followed by lab analysis.	Was the test method appropriate for the test substance? Water body is well studied and represents large freshwater food web.	**1**

Short citation (Author, year, or ID)	**MCGOL14A**		
Full citation (or link)	**McGoldrick, D.J., C. Chan, K.G. Drouillard, M.J. Keir, M.G. Clark, and S.M. Backus. 2014. Concentrations and trophic magnification of cyclic siloxanes in aquatic biota from the Western Basin of Lake Erie, Canada. Environmental Pollution 186:141-148.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test conditions (monitored and appropriate)	Data included representative samples of biological organisms representing different compartments of the Lake Erie food web. Walleye (*Sander vitreus*) provided by Ontario Ministry of Natural resources.	Were test conditions appropriate? Lake Erie is a well-studied lake and thus is appropriate for the study.	**2**
Consistency (across groups)	Laboratory testing conditions by use of various QA methods created consistency.	Were test conditions consistent across groups? No, sample sizes uneven among biological organisms in each food web compartment	**2**
Test organisms (if applicable)	Walleye (*Sander vitreus*) n = 15, ages 4-6 years Forage fish species (emerald shiner, trout perch, common shiner, white perch, yellow perch) Freshwater drum (*Aplodinotus grunniens*) Bulk zooplankton Mayfly larvae (*Hexagenia*) Physical and chemical characteristics of biological samples and sample sizes are presented in the supplemental information.	Was the inoculum or test organism appropriate? No, sample sizes uneven among biological organisms in each food web compartment. Biological characteristics in the SI include age, sex, length, and weight.	**3**
Controls	Laboratory is under positive pressure and physically separated from main laboratory space. Air entering laboratory is filtered, and access is restricted. All laboratory equipment and utensils pre-washed prior to use with hexane and acetone. Method blanks used in GC-MS prior to analyses and in-between samples. SI includes background levels of cVMSs in solvent and method blanks.	Were the appropriate controls used? Yes, the study used an appropriate amount of blanks and controls. However, these methods and controls are not standardized, nor have they been validated.	**2**
Duration	Not relevant to this study. Sampling was a one-time event rather than a time series monitoring study.	Was the duration of the study appropriate? Characterization of cVMS in environment was from one time point only, not designed as a long-term monitoring study.	**-**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Concentrations of siloxanes, food web biomagnification, trophic magnification factors	Were the appropriate outcomes reported? Yes	**1**

Short citation (Author, year, or ID)	**MCGOL14A**		
Full citation (or link)	**McGoldrick, D.J., C. Chan, K.G. Drouillard, M.J. Keir, M.G. Clark, and S.M. Backus. 2014. Concentrations and trophic magnification of cyclic siloxanes in aquatic biota from the Western Basin of Lake Erie, Canada. Environmental Pollution 186:141-148.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Control performance	Unknown	Was control performance acceptable? Some details available on control, but not on control performance	**3**
Sampling adequacy (frequency, duration)	Samples were collected in summer and fall in 2009.	Was the timing and frequency of sampling adequate? Only one sampling event was conducted.	**2**
Analytical method and measurements of test substance to verify presence in test system	Siloxane concentrations measured with GC-MS. Siloxane concentrations calculated relative to the surrogate 13C-labeled siloxanes. PCB180 analysis used a micro extraction technique followed by florisil chromatography and GC-ECD. Method performance assessed using fish tissue reference material. Surrogate recoveries determined by spiking samples with 13C-labelled PCB34. Lipids were quantified gravimetrically and were collected during the PCB extraction. Determined mean concentrations in reference samples and the recovery percentage for PCB34. Stable isotope ratios determined for all biota samples using an Isochrom continuous flow stable isotope mass spectrometer coupled to an elemental analyzer. Isotope values adjusted for lipid effects.	Were appropriate methods of analysis used? Yes, though control performance and QA details were not provided, so method reliability is not verified.	**2**
Results			
Confounding variables	Found that adjusting for lipid content only for the stable isotopes presented biased data; instead presented isotope values based on lipid content and moisture fraction. Contamination and volatilization are important confounding factors.	What sources of variability were noted and did they affect the outcome assessment? Yes, provided rationale for using a different method for using the lipid content. Several measures were taken to prevent contamination during sampling. Samples were taken back to the laboratory for further processing. While a number of precautions were taken to limit contamination, no mention of preventing volatilization was made.	**2**
Outcomes unrelated to exposure	None mentioned.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)? Not applicable	**1**

Short citation (Author, year, or ID)	**MCGOL14A**		
Full citation (or link)	**McGoldrick, D.J., C. Chan, K.G. Drouillard, M.J. Keir, M.G. Clark, and S.M. Backus. 2014. Concentrations and trophic magnification of cyclic siloxanes in aquatic biota from the Western Basin of Lake Erie, Canada. Environmental Pollution 186:141-148.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Data	Raw data tables not provided. D4 concentrations in biota: Plankton = ND (2 ng/g; limit of detection) Mayfly = 7 ng/g Fish 9-13 ng/g TMFs for D4: All species: 0.74 All species except plankton: 0.73 All species except plankton and walleye: 1.1 TMF >1 were observed for D4 and D5 in only 1 of 5 food web configurations and TMF for D6 were <1 in all cases. Data in SI includes mean and standard deviation for cVMS concentrations and PCB180, and the estimated trophic levels for all biological samples. Data is not raw data. Recovery percentages of spiked samples and presented lipid content is presented in the SI.	Were the data appropriately reported to document the outcome(s)? Yes, however raw data would be more appropriate. More data were presented in the supplemental information and was reviewed. SI data was not raw data.	**2**
Statistical method and kinetic calculations	Limit of detection determined using spiked samples replicates. Student's T test to determine limit of detection. Contaminant concentrations lipid normalized when specified. Means and standard deviations for concentrations and estimated trophic levels were used to estimate population distributions for each component of the food web. Contaminant concentrations approximate the arithmetic mean of the individuals in the homogenized samples. Standard deviation in these cases was estimated using the average coefficient of variation observed in the other components of the food web. TMFs were estimated using a probability based approach and then benchmarked against PCB180. Monte Carlo simulation used.	Were statistics and/or kinetic calculations described and consistent? Yes.	**1**

Short citation (Author, year, or ID)	**MCGOL14A**		
Full citation (or link)	**McGoldrick, D.J., C. Chan, K.G. Drouillard, M.J. Keir, M.G. Clark, and S.M. Backus. 2014. Concentrations and trophic magnification of cyclic siloxanes in aquatic biota from the Western Basin of Lake Erie, Canada. Environmental Pollution 186:141-148.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	SI includes input variables for the Monte Carlo simulations used to derive TMF distribution.		
Plausibility of results	Steps taken to prevent siloxane contamination of samples from other sources such as personal care products. Numerous quality control steps described.	Were the study results reasonable? Yes.	**1**
		Score (18–72); without two criteria, possible score was 16–60:	**31**

Short citation (Author, year, or ID)	**POWEL17A**		
Full citation (or link)	**Powell, D.E., N. Suganuma, K. Kobayashi, T. Nakamura, K. Ninomiya, K. Matsumura, N. Omura, and S. Ushioka. 2017. Trophic dilution of cyclic volatile methylsiloxanes (cVMS) in the pelagic marine food web of Tokyo Bay, Japan. Science of the Total Environment 578:366-382.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, and D6	Was the test substance identified definitively? No, samples were from the field. However, radiolabeled surrogate standards were used, and internal matrix control was used to verify cVMS concentrations.	**2**
Composition (purity, origin); single substance (not mixture)	Source: Not applicable; this is a field study Purity: Not applicable; this is a field study Single substance: Not applicable; this is a field study	Was the source and purity identified? No, samples were from the field. However, radiolabeled surrogate standards were used, and internal matrix control was used to verify cVMS concentrations.	**2**
Preparation	cVMS concentrations were determined from field samples and not prepared in the lab. Fish, sediment, and quality controls samples were collected November 2011. Sediments were collected from water depths ranging from 10 to 35 m using a Birge-Eckman grab sampler. After collection, sediment was removed from the sampler on deck using a clean acrylic core tube and the upper 1-cm of surface sediment was extruded into a stainless steel storage container that was sealed and stored on ice in the dark. Sediment in direct contact with the grab sampler was not retained. Associated field QC samples (Table S2) were collected by placing either blank sediment or reference sediment into a clean acrylic core tube and then treating the QC sample as a field sample. Fish were collected by commercial trawl and round haul. Targeted sampling occurred to ensure appropriate numbers and species were collected for each food web level. After collection, fish were measured for fresh weight and total length, and placed on ice for transport to the laboratory where they were stored at -30°C until processed. Associated field QC samples were collected	Was the test substance preparation described and appropriate for the test system? Substance preparation did not occur, but handling and storage of samples for cVMS analysis is more applicable and that was appropriate given the concerns for contamination. In addition, surrogate standards and internal matrix control were used.	**1**

Short citation (Author, year, or ID)	POWEL17A		
Full citation (or link)	**Powell, D.E., N. Suganuma, K. Kobayashi, T. Nakamura, K. Ninomiya, K. Matsumura, N. Omura, and S. Ushioka. 2017. Trophic dilution of cyclic volatile methylsiloxanes (cVMS) in the pelagic marine food web of Tokyo Bay, Japan. Science of the Total Environment 578:366-382.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	by attaching skin-on fillets from rainbow trout (*Oncorhynchus mykiss*) to the nets before deployment and then treating the QC sample as a fish that was captured during normal operation procedures. Japanese sea bass (*Lateolabrax japonicus*) and QC fillets were retained, stored, and processed as whole individual specimens. All other species were retained, stored, and processed as composite samples that consisted of 4 to 55 whole individual specimens. Whole-body homogenates of the individual or composite samples were prepared by passing each sample through a meat grinder twice. Isotopic signatures in fish were determined on the whole-body homogenate.		
Test Design			
Test system (suitability)	Field collection occurred in a defined 500 km^2 study area within Tokyo Bay, Japan. The defined study area covers approximately 55% of the inner portion of the bay. The estuary is divided into two sections by the 7 km wide narrows between Cape Kannon and Cape Futtsu, which impedes free exchange of seawater between the enclosed area of inner Tokyo Bay and the open sea. Inner Tokyo Bay is a eutrophic coastal region that has a surface area of about 922 km^2, is approximately 50 km in length and 20 km in width.	Was the test method appropriate for the test substance? Yes, the bay represents a well studies marine ecosystem representing numerous trophic levels. Tokyo Bay is a semi-closed estuary and represents a water body near a heavily industrialized city.	**1**
Test conditions (monitored and appropriate)	Samples of fish and sediment were analyzed for stable isotopic ratios of nitrogen ($^{15}N/^{14}N$; $\delta^{15}N$) and carbon ($^{13}C/^{12}C$; $\delta^{13}C$), which were used as continuous variables for estimating trophic level position occupied by each organism and for assessing the sources and flow of dietary carbon to consumers in the food web	Were test conditions appropriate? This is a field study, so the conditions were appropriate. The pelagic food web had been monitored previously.	**1**
Consistency (across groups)	The study area in Tokyo Bay was defined using a two-dimensional, a priori probability design based on 25 km^2 central aligned square grids.	Were test conditions consistent across groups? Yes, sample collection was consistent using a grid system and similar sediment samples were taken in various grid locations. Fish samples were non-	**3**

Short citation (Author, year, or ID)	**POWEL17A**		
Full citation (or link)	**Powell, D.E., N. Suganuma, K. Kobayashi, T. Nakamura, K. Ninomiya, K. Matsumura, N. Omura, and S. Ushioka. 2017. Trophic dilution of cyclic volatile methylsiloxanes (cVMS) in the pelagic marine food web of Tokyo Bay, Japan. Science of the Total Environment 578:366-382.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	Laboratory testing conditions by use of various QA methods created consistency.	specifically collected with a trawler, and specific biological samples were also targeted to represent all food web levels. However, fish were pooled into 1 to 3 composite samples each consisting of 4 to 55 individuals per composite, with the exception of Japanese seabass (*Lateolabrax japonicas*), which were treated as individual samples. More fish samples could have been collected and sample sizes could be more evenly distributed within the composite samples.	
Test organisms (if applicable)	Various fish species were collected and composite samples consist of combinations of the following species: Japanese sea bass (*Lateolabrax japonicus*), n=6 Red barracuda (*Sphyraena pinguis*), n=1 Chub mackerel (*Scomber japonicus*), n=1 Adult gizzard shad (*Konosirus punctatus*), n=1 Japanese anchovy (*Engraulis japonicus*), n=3 Japanese sardinella (*Sardinella zunasi*), n=3 Silver croaker (*Pennahia argentata*), n=3 Juvenile gizzard shad (*K. punctatus*), n=3	Was the inoculum or test organism appropriate? Yes. All other species were retained, stored, and processed as composite samples that consisted of 4 to 55 whole individual specimens. Whole-body homogenates of the individual or composite samples were prepared. Species collected represented various levels in the food web.	**2**
Controls	Polychlorinated biphenyl (PCB; CB-180) was used as a benchmark chemical to calibrate the food web and CB-153 as a reference chemical to validate the results. Special care was taken to avoid contamination and loss from evaporation/degradation during sample collection. Field QC for fish (Table S3) consisted of skin-on fillets from rainbow trout (*Oncorhynchus mykiss*) that were taken into the field, attached to the nets before deployment, and then treated as a sample. Field QC for sediment (Table S4) consisted of blank sediment that were taken into the field, placed into the core tube, and	Were the appropriate controls used? Yes. However, these methods and controls are not standardized, nor have they been validated.	**2**

Short citation (Author, year, or ID)	POWEL17A		
Full citation (or link)	Powell, D.E., N. Suganuma, K. Kobayashi, T. Nakamura, K. Ninomiya, K. Matsumura, N. Omura, and S. Ushioka. 2017. Trophic dilution of cyclic volatile methylsiloxanes (cVMS) in the pelagic marine food web of Tokyo Bay, Japan. Science of the Total Environment 578:366-382.		
Study type (e.g., OECD Guideline if applicable)	N/A		
Study Director (if applicable)	N/A		
GLP Compliance (if applicable)	N/A		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	then treated as a sample. Uncensored measured values were reported and used for all calculations even if the results were less than the levels of detection.		
Duration	Not relevant to study.	Was the duration of the study appropriate? Characterization of cVMS in environment was from one time point only, not designed as a long-term monitoring study.	-
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Bioaccumulation, trophic magnification factors (TMF), concentrations of cVMS, stable isotopes δ13C and δ15N, and various sediment parameters.	Were the appropriate outcomes reported? Methodology was appropriate to report outcomes of interest.	**1**
Control performance	Concentrations of cVMS in blank sediment taken into the field (N=9) and treated as samples were not statistically different (ANOVA; p>0.40) from concentrations in blank sediment that were retained in the laboratory (N=3), demonstrating that sediment samples were not contaminated by field methods. Concentrations of cVMS in skin-on fillets of blank fish taken into the field (N=5) and treated as samples were not statistically different (paired t-test; p>0.15) from concentrations in complement skin-on fillets of blank fish that were retained in the laboratory (N=5), demonstrating that fish were not contaminated by field methods.	Was control performance acceptable? Yes.	**1**
Sampling adequacy (frequency, duration)	Field sampling occurred during 1 period. Sediment samples were collected from 20 locations using a grid system. Biological samples represented various levels in the food web.	Was the timing and frequency of sampling adequate? The timing was appropriate but only one sampling period was conducted.	**3**
Analytical method and measurements of test substance to verify presence in test system	Sediment and biological samples were tested for isotopic nitrogen and carbon signatures. Sediment samples were characterized for total volatile matter (surrogate for organic matter), water content, bulk density, total organic carbon. Biological samples were tested for water content and lipid content.	Were appropriate methods of analysis used? Details were provided on origin of reference materials and internal standards.	**1**

Short citation (Author, year, or ID)	POWEL17A		
Full citation (or link)	Powell, D.E., N. Suganuma, K. Kobayashi, T. Nakamura, K. Ninomiya, K. Matsumura, N. Omura, and S. Ushioka. 2017. Trophic dilution of cyclic volatile methylsiloxanes (cVMS) in the pelagic marine food web of Tokyo Bay, Japan. Science of the Total Environment 578:366-382.		
Study type (e.g., OECD Guideline if applicable)	N/A		
Study Director (if applicable)	N/A		
GLP Compliance (if applicable)	N/A		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	Sediment samples were extracted then spiked with internal standards. In fish, extractions were performed before measuring cVMSs and PCB in whole body homogenates that were spiked with internal standards. GC-MS was used for determining cVMS concentrations, and high resolution GC-MS for PCB concentrations. Structure of the sampled food web was evaluated using δ15N and δ13C.		
Results			
Confounding variables	No attempt was made to control bias from variable exposure resulting from non-uniform movement of organisms across spatial concentration gradients, but the impacts of these confounding factors are discussed. Although bootstrap regression and benchmarking are valuable tools for calculation of TMF these methods cannot correct for bias that may exist in the sample data because spatial concentration gradients are present. This is a concern especially for chemicals having point-source emissions (for example, pharmaceutical and personal care products disposed to wastewater). Unfortunately methods to control for this potential bias, which is a complex function of exposure conditions and habitat utilization distributions of each organism across a study area, are not presently available and need to be developed. Modeling also illustrates that hydrophobic substances that biotransforms are most sensitive to the confounding impact of spatial concentration gradients, which may	What sources of variability were noted and did they affect the outcome assessment? Yes, multiple confounding factors were mentioned and discussion provided on this issues. For example, results also indicated that TMFs for the sampled food web may have been biased because of sample collection location and non-uniform patterns of organism movement across spatial concentration gradients. Other factors, such as fish mobility, home range, and age may also influence patterns of bioaccumulation. Field and vessel crew refrained from using personal care products that may contribute to sample contamination and wore nitrile gloves during sample handling.	**1**

Short citation (Author, year, or ID)	**POWEL17A**		
Full citation (or link)	**Powell, D.E., N. Suganuma, K. Kobayashi, T. Nakamura, K. Ninomiya, K. Matsumura, N. Omura, and S. Ushioka. 2017. Trophic dilution of cyclic volatile methylsiloxanes (cVMS) in the pelagic marine food web of Tokyo Bay, Japan. Science of the Total Environment 578:366-382.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	explain why bioaccumulation of D6 appeared to be different from D4 and D5.		
Outcomes unrelated to exposure	None mentioned.	Not applicable.	**-**
Data	Yes, raw data tables presented in the supplemental information. Sediment PCB concentrations were not determined in this study; rather PCB concentrations were summarized from existing literature. <u>Results summary</u>: Concentrations of cVMS and PCB in fish were variable among species and were not significantly correlated with lipid content. The lack of correlation indicated that biological accumulation of cVMS and PCB was not due to simple water-to-lipid partitioning (i.e., bioconcentration) alone, but was controlled by other processes such as exposure, dietary uptake (i.e., biomagnification), metabolism, assimilation efficiencies, and bioavailability. Isotopic signatures indicated that organisms in the sampled food web were feeding on a similar carbon source, which was significantly different from that measured in sediment. The narrow ranges observed for δ15N and δ13C signatures indicated that the sampled food web in Tokyo Bay was pelagic dominated and trophically compressed. There was no evidence from any of the regression models to suggest biomagnification of cVMS in Tokyo Bay. Rather, the regression models indicated that trophic dilution of cVMS, not trophic magnification, occurred.	Were the data appropriately reported to document the outcome(s)? Yes.	**1**

Short citation (Author, year, or ID)	POWEL17A		
Full citation (or link)	Powell, D.E., N. Suganuma, K. Kobayashi, T. Nakamura, K. Ninomiya, K. Matsumura, N. Omura, and S. Ushioka. 2017. Trophic dilution of cyclic volatile methylsiloxanes (cVMS) in the pelagic marine food web of Tokyo Bay, Japan. Science of the Total Environment 578:366-382.		
Study type (e.g., OECD Guideline if applicable)	N/A		
Study Director (if applicable)	N/A		
GLP Compliance (if applicable)	N/A		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	Modeling suggests that dietary uptake may account for greater than 80% of the accumulation of hydrophobic chemicals (log KOW N 6) by organisms that occupy trophic positions greater than TL=3. Part of the work was to compare two statistical models in their TMF calculations. Here, bootstrap regression models that incorporated benchmarking were considered superior to OLS regression models because they: 1) were effective at reducing bias from experimental design, 2) had the potential to control bias resulting from food web dynamics and trophic level structure, 3) improved fit of the regression models and reduced overall uncertainty, and 4) generated TMF values that were based on a calibrated food web. Neither bootstrap or OLS regression can control for bias that exists in the sample data, such as may occur because of variable exposure across spatial concentration gradients.		
Statistical method and kinetic calculations	A Type I error (α) of 0.05was used to judge the significance of all statistical tests. The study area was defined using a two-dimensional a priori probability design based on 25 km^2 central aligned square grids that extended seaward from the head of the bay towards the narrows between Cape Kannon and Cape Futtsu. Trophic magnification factors (TMFs) were calculated from slopes of ordinary least-squares (OLS) regression models and slopes of bootstrap regression models, which were used as robust alternatives to the OLS models. Bootstrap regression was performed using bivariate Monte-Carlo resampling (n=10,000 trials, with replacement) of probability density functions (PDF) that	Were statistics and/or kinetic calculations described and consistent? Provided details on why all measurements were necessary and how stats were used/selected.	**1**

Short citation (Author, year, or ID)	**POWEL17A**		
Full citation (or link)	**Powell, D.E., N. Suganuma, K. Kobayashi, T. Nakamura, K. Ninomiya, K. Matsumura, N. Omura, and S. Ushioka. 2017. Trophic dilution of cyclic volatile methylsiloxanes (cVMS) in the pelagic marine food web of Tokyo Bay, Japan. Science of the Total Environment 578:366-382.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	were defined for each species, based on the TMF regression model. One-Way Analysis of Variance (ANOVA) from summary data was used to test for differences between results for Tokyo Bay and results reported by other studies for slopes and log-transformed concentrations. Limit of detection during analysis of samples (defined in Table S2) were calculated as a function of the variance associated with replicate analyses of reagent blanks, low-level standards, and samples.		
Plausibility of results	All controls well-documented, and agreed with previous published literature.	Were the study results reasonable? Yes, the present study provided evidence that trophic dilution of cVMS, not trophic magnification, occurred across for the pelagic marine food web in Tokyo Bay, but sample size was low with 1 to 6 samples per fish type. The concentration of D4 vs. N isotope showed a downward trend, but had a low R^2 value (0.10). However, the results for Tokyo Bay were in agreement with results from at least 6 of 10 other food web studies, suggesting that trophic dilution of cVMS was not likely related to type of food web (pelagic vs demersal), environment (marine vs freshwater), species composition, or location.	**2**
		Score (18–72); without 2 criteria, possible score was 16–64:	**25**
Note: peer reviewed version of DOWCO12A (sponsor study version). DOWCO12A was not available for review.			

Short citation (Author, year, or ID)	**POWEL18A**		
Full citation (or link)	**Powell, D.E., M. Schøyen, S. Øxnevad, R. Gerhards, T. Böhmer, M. Koerner, J. Durham, and D.W. Huff. 2018. Bioaccumulation and trophic transfer of cyclic volatile methylsiloxanes (cVMS) in the aquatic marine food webs of the Oslofjord, Norway. Science of The Total Environment 622: 127-139.**		
Study type (e.g., OECD Guideline if applicable)	**N/A**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
		Score (18–72):	**N/A**
Note: peer reviewed version of DOWCO10B. Study not reviewed as more detail provided in the sponsor study version.			

Short citation (Author, year, or ID)	**MCGOL14B**		
Full citation (or link)	**McGoldrick, D.J., R.J. Letcher, E. Barresi, M.J. Keir, J. Small, M.G. Clark, E. Sverko, and S.M. Backus. 2014. Organophosphate flame retardants and organosiloxanes in predatory freshwater fish from locations across Canada. Environmental Pollution 193 (2014):254-261.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	Use of cVMSs not described. Radiolabeled compounds, 13C-D4, 13C-D5, 13C-D6, were used as internal standards	Was the test substance identified definitively? No, samples were from the field. However, internal standards were used to verify cVMS concentrations.	**2**
Composition (purity, origin); single substance (not mixture)	Source: Not applicable; this is a field study Origin: Not applicable; this is a field study Purity: Not applicable; this is a field study	Was the source and purity identified? No details provided on source of organosiloxanes	**3**
Preparation	Fish were collected from 16 water bodies across Canada consisting of lakes, rivers, and reservoirs. However, the data used for Samples for organosiloxane analysis was collected only from Lakes Ontario, Erie, Huron, Superior, Winnipeg, Athabasca, and Kusawa. All water bodies are part of the monitoring network used by Environment Canada. Lakes range from minimally to heavily influenced by humans activities. Fish were collected using bottom set grill nets in 2009 or 2010 between June and October, with exception for two lakes that had fish collected in December. Lake trout were the most commonly collected fish for the monitoring program by Environment Canada, with walleye collected when lake trout were not available. Fish were frozen as soon as possible, shipped to laboratory storage, and frozen until processing. Fish were partially thawed, weighed, measured for length, and sexed. Fish were homogenized per individual fish. Glass materials were preferred over plastic in the laboratory. Biological samples were analyzed for organosiloxane concentrations using a comparison to radiolabeled organosiloxane spiked samples.	Was the test substance preparation described and appropriate for the test system? Substance preparation did not occur; handling and storage of samples for cVMS analysis is more applicable. Details on methods used to avoid sample contamination were not described. Supplemental information file includes list of water bodies, species, and number of fish analyzed for siloxanes.	**3**
Test Design			

Short citation (Author, year, or ID)	**MCGOL14B**		
Full citation (or link)	**McGoldrick, D.J., R.J. Letcher, E. Barresi, M.J. Keir, J. Small, M.G. Clark, E. Sverko, and S.M. Backus. 2014. Organophosphate flame retardants and organosiloxanes in predatory freshwater fish from locations across Canada. Environmental Pollution 193 (2014):254-261.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test system (suitability)	Field collection in Canadian freshwater bodies followed by lab analysis. Fish captured using bottom set gill nets in 2009 or 2010 between June and October.	Was the test method appropriate for the test substance? Yes	**1**
Test conditions (monitored and appropriate)	Data included biological samples from five water bodies in Canada. Samples were analyzed for cVMS using a comparison to radiolabeled organosiloxane spiked samples.	Were test conditions appropriate? This is a field study, so test conditions were appropriate. Many of these water bodies are well documented and are appropriate.	**1**
Consistency (across groups)	Samples sizes among water bodies were not consistent.	Were test conditions consistent across groups? No, fish sample sizes were not consistent among water bodies sampled.	**3**
Test organisms (if applicable)	Lake trout (*Salvelinus namaycush*) Walleye (*Sander vitreus*) Age: unknown When lake trout were not available at a sampling location, walleye were captured. Supplemental information contains additional biological data such as collection year, water body, total length, total weight, sex, and age for each fish.	Was the inoculum or test organism appropriate? Yes, both species are piscivorous and represent organisms found in upper trophic levels.	**2**
Controls	Fish tissue samples were fortified with D4, D5, and D6 used in previous work by the same research team and was analyzed with every batch of whole fish homogenate samples (n=11) and was used as a reference material. Method blanks consisted of an internal standard. Average recovery was determined. Solvent blanks used. Glassware used when possible in the laboratory. Supplemental information includes solvent method blank concentrations present in fish above the MDL and the estimated MLOQs and MLODs for the siloxane target compounds.	Were the appropriate controls used? Yes, however no mention of field blanks or negative control blanks.	**2**

Short citation (Author, year, or ID)	**MCGOL14B**		
Full citation (or link)	**McGoldrick, D.J., R.J. Letcher, E. Barresi, M.J. Keir, J. Small, M.G. Clark, E. Sverko, and S.M. Backus. 2014. Organophosphate flame retardants and organosiloxanes in predatory freshwater fish from locations across Canada. Environmental Pollution 193 (2014):254-261.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Duration	Not relevant to this study. Sampling was a one-time event rather than a time series monitoring study.	Was the duration of the study appropriate? Characterization of cVMS in environment was from one time point only, not designed as a long-term monitoring study.	**-**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Organosiloxane concentrations were determined in fish tissues collected from the field.	Were the appropriate outcomes reported? Yes	**1**
Control performance	Control performance was documented. Mean concentrations of 10 repeated measured of D4, D5, and D6 were within one standard deviation of the consensus values reported for the same material used in an inter-laboratory comparison study of siloxanes in fish homogenate.	Was control performance acceptable? Yes	**1**
Sampling adequacy (frequency, duration)	Fish were collected using bottom set grill nets in 2009 or 2010 between June and October, with exception for two lakes that had fish collected in December. Fish samples collected for organosiloxane analyses were collected from water bodies across Canada. The majority of the samples were collected from the Great Lakes area and two additional water bodies located in northwestern Canada (Lakes Kusawa and Athabasca). Additional analyses were conducted for flame retardants and those fish samples came from additional water bodies across Canada. Fish samples frozen as soon as possible after capture and shipped to a laboratory and stored in the freezer until further processing. Fish were partially thawed prior to processing, measured for length, weight, sex, and aging structures were removed. Individual fish were cut into pieces and homogenized. 3-10 fish were selected from each sampling station for chemical analysis. Whole body homogenate samples of lake trout and walleye screened for flame retardants and organosiloxanes.	Was the timing and frequency of sampling adequate? No, only one sampling event was conducted.	**3**

Short citation (Author, year, or ID)	**MCGOL14B**		
Full citation (or link)	**McGoldrick, D.J., R.J. Letcher, E. Barresi, M.J. Keir, J. Small, M.G. Clark, E. Sverko, and S.M. Backus. 2014. Organophosphate flame retardants and organosiloxanes in predatory freshwater fish from locations across Canada. Environmental Pollution 193 (2014):254-261.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Analytical method and measurements of test substance to verify presence in test system	Extraction occurred in a clean room facility and spiked with a surrogate standard. A gas chromatograph (GC) coupled with a mass selective (MS) detector was used. Supplemental information includes optimized parameters used in GC-MS.	Were appropriate methods of analysis used? Yes, though no validation of method.	**1**
Results			
Confounding variables	Variability limited by collecting fish samples from various water bodies using the same methods, storage in the same bags at the same temperatures, and homogenizing samples at the same facility. No evidence that significant contamination is in the dataset though used one water body sample with the lowest fish tissue concentrations as the background sample with other stations compared to this sample. Contamination and volatilization are important confounding factors for D4 studies. No methods were discussed to reduce contamination of samples in the field or lab by personnel. Rather, the study notes that: while contamination of the samples with siloxane materials is a possibility at any step in the process (collection, storage, processing) other studies have reported these to be low for the field component. There is no evidence of significant contamination in our dataset; however, for the purpose of this study, the levels observed at the northern most and “least impacted” location, Kusawa Lake, will be considered as background and other stations compared to it.	What sources of variability were noted and did they affect the outcome assessment? Authors noted potential for potential issues and discussed; concluded that any confounding factors were unlikely to affect the results. No contamination control measures were used in the field or lab to reduce contamination of the samples by personnel.	**3**

Short citation (Author, year, or ID)	**MCGOL14B**		
Full citation (or link)	**McGoldrick, D.J., R.J. Letcher, E. Barresi, M.J. Keir, J. Small, M.G. Clark, E. Sverko, and S.M. Backus. 2014. Organophosphate flame retardants and organosiloxanes in predatory freshwater fish from locations across Canada. Environmental Pollution 193 (2014):254-261.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Outcomes unrelated to exposure	None mentioned.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)? Not applicable.	**-**
Data	No, raw data tables not reported. Results summary: D4, D5, and D6 were detected at levels above detection limits in all 87 fish samples. The most abundant siloxanes, D4, D5, and D6,were present at measureable but low levels in nearly all procedural solvent blanks and averaged 0.81 ng/g D4. The levels of D4, D5, and D6 in fish were highest in the Laurentian Great Lakes particularly in Lake Trout from Lake Ontario and the eastern basin of Lake Erie. Lake Ontario had the highest siloxane values, with D4 ranging 2.5 – 28 ng/g ww.	Were the data appropriately reported to document the outcome(s)? Raw data tables were not provided.	**3**
Statistical method and kinetic calculations	Percent coefficient of variation for repeated measures of dose fish tissue was determined. Method limit of detection and method limit of quantification determined. Supplemental information includes Kaplan-Meier summary statistics for D4, D5, and D6 concentrations in lake Trout or Walleye.	Were statistics and/or kinetic calculations described and consistent? Yes	**1**
Plausibility of results	Ranges of concentrations found in the environment and similar to those measured in other work. Steps taken to prevent siloxane contamination of samples. Numerous quality control steps described.	Were the study results reasonable? Yes, however, no methods were made to	**1**
		Score (18–72); without two criteria, possible score was 16–60:	**31**

Short citation (Author, year, or ID)	**CUI19A and CUI19B (SI)**		
Full citation (or link)	**Cui, S., Q. Fu, L. An, T. Yu, F. Zhang, S. Gao, D. Liu, D. and H. Jia. 2019. Trophic transfer of cyclic methyl siloxanes in the marine food web in the Bohai Sea, China. Ecotoxicology and Environmental Safety 178: 86–93.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	Standard samples of D4, D5 and D6 were acquired from Tokyo Chemical Industry (Wellesley Hills, MA, USA), and D7 was acquired from Sigma-Aldrich (St. Louis, MO, USA).	Was the test substance identified definitively? No, samples were from the field. However, internal standards were used to verify cVMS concentrations and details were provided for the standards.	**3**
Composition (purity, origin); single substance (not mixture)	Source: Not applicable; this is a field study Origin: Not applicable; this is a field study Purity: Not applicable; this is a field study	Was the source and purity identified? No details provided on source of organosiloxanes	**3**
Preparation	Marine organisms (a total of 518 individuals (excluded zooplankton) make up 151 samples) were collected from coastal area of the North Bohai Sea in September and October 2014. The collected organisms included two seabird species (Saunder's gull and Herring gull), five fish species (Monkfish, Moray, Goby, Joyner's tonguesole and Hairtail), six crustacean species (Chinese shrimp, Whiskered velvet shrimp, Mantis shrimp, Japanese stone crab, Japanese stone crab and Swimming crab), four mollusc species (Cockles, Naticidae, *Rapana venosa* and Short-necked clam), and the primary producer (zooplankton). Larger organisms (*e.g.*, ≥10 g of muscle or soft tissue per individual) were analyzed as individual samples. Smaller organisms (<10 g of soft tissue or muscle per sample), were composited to ensure sufficient mass for analysis.	Was the test substance preparation described and appropriate for the test system? Substance preparation did not occur; handling and storage of samples for cVMS analysis is more applicable. Details on methods used to avoid sample contamination was described in the SI and included not using personal care products 24 hours prior to sampling, wearing gloves, and cites two studies (Hong et al. 2014 and Jia et al. 2015 for developing protocols for avoiding contamination). Supplemental information file includes sampling locations.	**1**
Test Design			
Test system (suitability)	Field collection in the Bohai Sea followed by lab analysis. The zooplankton collection was followed the methods of HY003.4–91 (China) with the collection net of 32 cm (mesh: 0.096 mm)	Was the test method appropriate for the test substance? Yes	**1**

Short citation (Author, year, or ID)	**CUI19A and CUI19B (SI)**		
Full citation (or link)	**Cui, S., Q. Fu, L. An, T. Yu, F. Zhang, S. Gao, D. Liu, D. and H. Jia. 2019. Trophic transfer of cyclic methyl siloxanes in the marine food web in the Bohai Sea, China. Ecotoxicology and Environmental Safety 178: 86–93.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	in diameter, fish and invertebrates were caught with a bottom trawl, and sea birds were captured by a fowler folder. The muscles of fish and seabird, the soft tissues of invertebrates and the whole bodies of zooplankton were collected for chemical and isotope analysis. Sampling followed methods presented in Ma et al. (2013)		
Test conditions (monitored and appropriate)	Data included biological samples the Bohai Sea in China. Samples were analyzed for cVMS using a comparison to organosiloxane spiked samples.	Were test conditions appropriate? This is a field study, so test conditions were appropriate. Many of these water bodies are well documented and are appropriate.	**1**
Consistency (across groups)	Samples sizes were not consistent. 10 g of tissue was used, regardless if this was from one organism or multiple. No consistency on compositing samples.	Were test conditions consistent across groups? No, tissue samples were not consistent.	**3**
Test organisms (if applicable)	18 species were used in this study, but uneven sample numbers were collected among species. For example, 5 Lauder's gull were collected, and 140 short-necked clams. Species: Saunder's gull, Herring gull), five fish species: Monkfish, Moray, Goby, Joyner's tonguesole and Hairtail, six crustacean species: Chinese shrimp, Whiskered velvet shrimp, Mantis shrimp, Japanese stone crab, Japanese stone crab and Swimming crab, four mollusc species: Cockles, Naticidae, *Rapana venosa* and Short-necked clam, primary producer (zooplankton).	Was the inoculum or test organism appropriate? Yes, species are representative organisms found in various trophic levels, though more detail on species collection is needed.	**2**

Short citation (Author, year, or ID)	**CUI19A and CUI19B (SI)**		
Full citation (or link)	**Cui, S., Q. Fu, L. An, T. Yu, F. Zhang, S. Gao, D. Liu, D. and H. Jia. 2019. Trophic transfer of cyclic methyl siloxanes in the marine food web in the Bohai Sea, China. Ecotoxicology and Environmental Safety 178: 86–93.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	No additional biological data such as collection year, water body, total length, total weight, sex, and age for each organism was presented.		
Controls	Controls and replicate spike samples were used. D4-D7 were detected in all blanks and that all data were blank corrected. The SI states that a field blank for every 10 biota samples was collected in the field.	Were the appropriate controls used? Yes.	**1**
Duration	Not relevant to this study. Sampling was a one-time event rather than a time series monitoring study.	Was the duration of the study appropriate? Characterization of cVMS in environment was from September and October 2014, not designed as a long-term monitoring study.	**-**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Organosiloxane concentrations were determined in fish tissues collected from the field.	Were the appropriate outcomes reported? Yes	**1**
Control performance	Control performance was documented. The mean recoveries were reported.	Was control performance acceptable? Yes. Analytical controls were acceptable.	**1**
Sampling adequacy (frequency, duration)	In this study, marine organisms (a total of 518 individuals (excluding zooplankton) make up 151 samples) were collected from four locations in the coastal area of the North Bohai Sea in September and October 2014. No details were provided on sample transport and storage. No details on measurements such as length, weight, and sex were reported. Measurements included TMF, trophic dilution.	Was the timing and frequency of sampling adequate? Yes, only one sampling event (September and October 2014) was conducted.	**2**
Analytical method and measurements of test substance to verify presence in test system	A spiked surrogate standard was used. A gas chromatograph (GC) coupled with a mass selective (MS) detector was used. Sample treatment was conducted in a clean air cabinet.	Were appropriate methods of analysis used? Yes. Method was validated using methods from previous publications and included the use of blanks, spike recoveries, and relative standard deviation (RSD).	**1**

Short citation (Author, year, or ID)	**CUI19A and CUI19B (SI)**		
Full citation (or link)	**Cui, S., Q. Fu, L. An, T. Yu, F. Zhang, S. Gao, D. Liu, D. and H. Jia. 2019. Trophic transfer of cyclic methyl siloxanes in the marine food web in the Bohai Sea, China. Ecotoxicology and Environmental Safety 178: 86–93.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	Validated calibration methods for PBDEs as same as those in another study (Jia et al. 2011).		
Results			
Confounding variables	Variability may be impacted by use of composite samples, , which may include one or multiple organisms. Contamination and volatilization are important confounding factors for D4 studies. Protocols were used to reduce contamination of samples in the field or lab by personnel.	What sources of variability were noted, and did they affect the outcome assessment? Authors stated that they could not ensure that the sampling locations had similar concentrations of cVMS, which can bias calculated TMF Authors also noted that isotopic values indicated the two species of birds were likely feeding at different food webs, which led the authors to calculate TMF with and without inclusion of bird data. Some contamination control measures were used in the field or lab to reduce contamination of the samples by personnel.	**3**
Outcomes unrelated to exposure	None mentioned.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)? Not applicable.	**-**
Data	No, raw data tables not reported. <u>Results summary</u>: The trophic magnification factors (TMF) for D4 to D7 were 1.7 (95% confidence interval: 1.1–2.6), 3.5 (2.5–5.0), 1.8 (1.3–2.6), and 0.63 (0.40–0.99) respectively, for the zooplankton-invertebrate-fish-bird based food web, with significant biomagnification observed for D4, D5 and D6, and a significant negative relationship for D7. Calculated TMF for D4 to D7 were 1.4 (95% confidence interval: 0.82-2.3), 3.0 (1.9-4.7), 1.3 (0.85-2.0), and 0.40 (0.23-0.69) respectively, for the zooplankton-invertebrate-fish food chain, with significant biomagnification for D5, a significant negative relationship for D7, but no significant relationship for D4 or D6.	Were the data appropriately reported to document the outcome(s)? Raw data tables were not provided.	**3**
Statistical method and kinetic calculations	TMF values were calculated using a standard and an alternative approach for comparison. Details are presented in the SI.	Were statistics and/or kinetic calculations described and consistent? Yes	**1**

Short citation (Author, year, or ID)	**CUI19A and CUI19B (SI)**		
Full citation (or link)	**Cui, S., Q. Fu, L. An, T. Yu, F. Zhang, S. Gao, D. Liu, D. and H. Jia. 2019. Trophic transfer of cyclic methyl siloxanes in the marine food web in the Bohai Sea, China. Ecotoxicology and Environmental Safety 178: 86–93.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	Evaluations on how the results were affected by different treatment of non-detected results were conducted - TMF values were estimated using 3 methods to address the treatment of non-detected results.		
Plausibility of results	Ranges of concentrations found in the environment are similar to those measured in other work. Steps taken to prevent siloxane contamination of samples. Quality control steps described.	Were the study results reasonable? Yes, results are considered plausible given the controls and sampling methods used.	**1**
		Score (18–72); without two criteria, possible score was 16–64:	**28**

Short citation (Author, year, or ID)	**DOW14A**		
Full citation (or link)	**Powell, D.E. 2014. Interim Report—Trophic Transfer of Cyclic Volatile Methylsiloxanes (cVMS) and selected Polychlorinated Biphenyl (PCB) across the aquatic food web of Lake Champlain, USA. HES Study No.: 12349-108. Dow Corning, Auburn, MI. November.**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**Powell, D.E.**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4, D5, and D6	Was the test substance identified definitively? Yes, CAS numbers used.	**1**
Composition (purity, origin); single substance (not mixture)	Origin: no details provided Purity: no details provided The study refers the reader to two previously published sponsor studies that were used for method development.	Was the source and purity identified? No information on purity	**2**
Preparation	No details provided on the use of cVMS as controls or field blanks.	Was the test substance preparation described and appropriate for the test system? Not enough details were provided.	**3**
Test Design			
Test system (suitability)	Lake Champlain is a long (200 km), narrow (19 km at widest point) and deep (maximum depth 122 m; average depth 19.5 m) lake that has a surface area of 1130 km2 and a volume of 26 km^3. Seven trophic guilds were incorporated into the food web, including, primary producers, detritivores, herbivores, algivores, planktivores, invertivores, and piscivores.	Was the test method appropriate for the test substance? Yes; the water body represents a food web with numerous trophic guilds.	**1**
Test conditions (monitored and appropriate)	Surface sediments and biota were collected from across the defined 800 km2 study area 22-29 October 2012. Surface sediments were collected from water depths of 6.4 to 114 m by systematic sampling at each sample collection station, which is the preferred experimental design for estimating means, totals, and patterns of contamination (Gilbert 1987). Replicate samples of surface sediment were not collected. Samples of the aquatic food web were collected from 13 locations across 6 sites in the defined study of the main lake basin. Biota samples were collected by bottom trawl, mid-water trawl, and plankton haul that were deployed to	Were test conditions appropriate? Yes, details were provided on sampling details and a span of sampling events occurred across the entire lake.	**2**

Short citation (Author, year, or ID)	**DOW14A**		
Full citation (or link)	**Powell, D.E. 2014. Interim Report—Trophic Transfer of Cyclic Volatile Methylsiloxanes (cVMS) and selected Polychlorinated Biphenyl (PCB) across the aquatic food web of Lake Champlain, USA. HES Study No.: 12349-108. Dow Corning, Auburn, MI. November.**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**Powell, D.E.**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	specifically sample the dominate populations of species in the food web.		
Consistency (across groups)	Special care and precautions were taken to avoid contamination and loss from evaporation and degradation during sample collection, storage and analysis.	Were test conditions consistent across groups? Yes, protocols were used to reduce sample contamination.	**1**
Test organisms (if applicable)	A total of n=59 samples of surface sediment collected from n=59 locations across the defined study area of the lake were used to evaluate spatial variability across the defined study area. A total of n=5 to 11 samples (pooled or individual) were collected for each species, however not all species were collected at each site (n=0 to 6 samples per species). The sampled food web included zooplankton, mysid shrimp (*Mysis relicta*), and ten species of finfish with lake trout (*Salvelinus namaycush*) representing the top piscivorous species. Benthic macro invertebrates were not collected.	Was the inoculum or test organism appropriate? Yes, seven levels in the food web were sampled.	**1**
Controls	Concentrations of cVMS in sediment were measured in extracts of wet sediment that were spiked with internal standards. Concentrations of cVMS and PCB in fish were measured in extracts of whole-body homogenates that were spiked with internal standards.	Were the appropriate controls used? Yes	**1**
Duration	Multiple sediment and biota sampling events between October 22-29, 2012.	Was the duration of the study appropriate? Yes	**1**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Trophic magnification factor (TMF); sediment samples were characterized for water content, total volatile matter (a surrogate measure of organic matter), bulk density, and total organic carbon (TOC). Biological samples were characterized for water content and lipid content. Sediment and biota were also characterized for isotopic signatures of nitrogen (N; 15N) and carbon (C; 13C).	Were the appropriate outcomes reported? Yes	**1**

Short citation (Author, year, or ID)	**DOW14A**		
Full citation (or link)	**Powell, D.E. 2014. Interim Report—Trophic Transfer of Cyclic Volatile Methylsiloxanes (cVMS) and selected Polychlorinated Biphenyl (PCB) across the aquatic food web of Lake Champlain, USA. HES Study No.: 12349-108. Dow Corning, Auburn, MI. November.**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**Powell, D.E.**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Control performance	Control performance not reported.	Was control performance acceptable? Not quantified – data should be provided.	**2**
Sampling adequacy (frequency, duration)	Yes, a large sample size of sediment (n=59) and for each species, replicates were collected (n=5-11)	Was the timing and frequency of sampling adequate? Yes	**1**
Analytical method and measurements of test substance to verify presence in test system	Concentrations in extracts of fish and sediment were quantified for cVMS and PCB using gas chromatography/quadrupole mass spectrometry or high-resolution gas chromatography/high-resolution mass spectrometry, respectively. Concentrations of cVMS in sediment were measured in extracts of wet sediment that were spiked with internal standards. Concentrations of cVMS and PCB in fish were measured in extracts of whole-body homogenates that were spiked with internal standards.	Were appropriate methods of analysis used?	**1**
Results			
Confounding variables	Special care and precautions were taken to avoid contamination and loss from evaporation and degradation during sample collection, storage and analysis. Zooplankton were not used for the TMF calculations because stable isotope data was inconsistent and not in agreement with the rest of the sampled food web. The stable isotope results for zooplankton appeared to be biased because samples were collected during the fall overturn of the lake and large quantities of seston and detritus, presumably originating from the nepheloid layer of bottom sediment, were collected. Consequently, it was assumed that concentrations of cVMS and PCB were also biased and results for zooplankton were not used for calculation of TMF.	What sources of variability were noted and did they affect the outcome assessment?	**1**
Outcomes unrelated to exposure	None reported.	Were there differences among the study groups unrelated to exposure that influenced the outcome(s)? Not applicable	**-**

Short citation (Author, year, or ID)	**DOW14A**		
Full citation (or link)	**Powell, D.E. 2014. Interim Report—Trophic Transfer of Cyclic Volatile Methylsiloxanes (cVMS) and selected Polychlorinated Biphenyl (PCB) across the aquatic food web of Lake Champlain, USA. HES Study No.: 12349-108. Dow Corning, Auburn, MI. November.**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**Powell, D.E.**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Data	No, raw data tables were not provided. Authors reported that uncensored measured values were used for all calculations even if reported results were less than the reported limits of detection. Results summary: Concentrations of cVMS in biota were highly variable within and between species, and generally appeared to be related to sample collection location.	Were the data appropriately reported to document the outcome(s)?	**2**
Statistical method and kinetic calculations	TMF were derived from ordinary least-squares(OLS) regression models and bootstrap regression models, For Probabilistic methods were used to control bias resulting from experimental design; benchmarking was used to control bias resulting from food web dynamics and trophic level structure; and exposure correction was used to control bias resulting from variable exposure across concentration gradients. OLS and bootstrap regressions for D4 were not significant.	Were statistics and/or kinetic calculations described and consistent? Yes, good documentation of statistics used.	**1**
Plausibility of results	Reliable trophic magnification factors (TMFs) could not be obtained for cVMS or PCB in the aquatic food web of Lake Champlain. Experimental sampling design, concentration gradients, and species migration patterns across a study area have a large impact on the determination of TMF. The complexity of Lake Champlain and the occurrence of concentration gradients and variable species migrations patterns across the study area, were likely the major contributing factors that prevented reliable field TMFs to be obtained. This situation was further complicated by the experimental sampling design, which did not include collection of benthic macro invertebrates and allowed samples to be collected from numerous areas in the lake rather than	Were the study results reasonable? Yes, and the study also explained why TMF results could not be determined.	**1**

Short citation (Author, year, or ID)	DOW14A		
Full citation (or link)	Powell, D.E. 2014. Interim Report—Trophic Transfer of Cyclic Volatile Methylsiloxanes (cVMS) and selected Polychlorinated Biphenyl (PCB) across the aquatic food web of Lake Champlain, USA. HES Study No.: 12349-108. Dow Corning, Auburn, MI. November.		
Study type (e.g., OECD Guideline if applicable)	N		
Study Director (if applicable)	Powell, D.E.		
GLP Compliance (if applicable)	N		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	limiting sample collection to the areas of highest exposure. Modeling illustrated that study areas with homogenous exposure conditions and concentrations are best suited to determine TMFs that accurately represent the bioaccumulative properties of cVMS and other substances.		
		Score (18–72); without one criterion, possible score was 17-68:	**23**

Short citation (Author, year, or ID)	**RUUS19A**		
Full citation (or link)	**Ruus A., K. Bæk, T. Rundberget, I. Allan, B. Beylich, M. Schlabach, N. Warner, K. Borgå, and M. Helberg 2019. Environmental contaminants in an urban fjord, 2018. RAPPORT L.NR. 7410-2019. Norwegian Institute for Water Research.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Government report.**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	Multiple contaminants (metals, PCBS, etc.) including siloxanes (D4, D5, and D6).	Was the test substance identified definitively? No, samples were from the field. However, standards were used, though no details were provided on the standards.	**3**
Composition (purity, origin); single substance (not mixture)	Source: Not applicable; this is a field study Purity: Not applicable; this is a field study Single substance: Not applicable; this is a field study	Was the source and purity identified? No, samples were from the field. However, standards and field and reference blanks were used, though no specific details were provided on the use of standards.	**2**
Preparation	cVMS concentrations were determined from field samples and not prepared in the lab. Samples for cVMS analysis included herring gull blood and eggs, cod liver, sludge, and miscellaneous biota (Table 9). NILU's laboratories are accredited by Norwegian Accreditation for ISO/IEC 17025. NILU is not accredited for the analysis of PFRs, but the same quality assurance procedures (as for the accredited compounds) were applied for the analyses of these compounds. NILU's laboratories are accredited by Norwegian Accreditation for ISO/IEC 17025. NILU is not accredited for the analysis of siloxanes. However, to the extent possible, documentation, preparation, analysis and calculations were performed in accordance with accredited methods. NILU has previously participated in a laboratory intercalibration of siloxanes (McGoldrick et al. 2011) and has also worked closely with the industry in Artic monitoring programs to develop methods to enhance result accuracy and limit reporting of false positives (Warner et al. 2013). NILU has extensive experience with analysis of siloxanes. The greatest risk in the analysis is background contamination, as these chemicals (D4, D5 and D6) are applied in e.g. skin care products. Using a state-of-the-art cleanroom and clean bench technologies, NILU is	Was the test substance preparation described and appropriate for the test system? Substance preparation did not occur but handling and storage of samples for cVMS analysis is more applicable. No details are provided on the transport and storage of samples. Personal care products were not used by staff prior to sampling.	**2**

Short citation (Author, year, or ID)	**RUUS19A**		
Full citation (or link)	**Ruus A., K. Bæk, T. Rundberget, I. Allan, B. Beylich, M. Schlabach, N. Warner, K. Borgå, and M. Helberg 2019. Environmental contaminants in an urban fjord, 2018. RAPPORT L.NR. 7410-2019. Norwegian Institute for Water Research.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Government report.**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	capable of performing trace analysis of these compounds in matrices from pristine environments, including the Arctic (Krogseth et al. 2013; Warner et al. 2013).		
Test Design			
Test system (suitability)	Field collection of representatives of the marine food web in the inner Oslofjord, Norway in 2018 (various collection dates), followed by lab analysis.	Was the test method appropriate for the test substance? Yes, the inner Oslofjord in Norway is well characterized and is appropriate for sampling the marine food web.	**1**
Test conditions (monitored and appropriate)	Data included representatives of the pelagic food web in from the Oslofjord. However, samples (cod, sludge, herring) may not accurately represent all levels in the food web.	Were test conditions appropriate? This is a field study, so the conditions were appropriate. The pelagic food web had been monitored for several years, however a greater variety of organisms should be sampled.	**2**
Consistency (across groups)	Laboratory testing conditions with QA created consistency. Samples were extracted and analyzed in batches with a minimum of 3 procedural blanks to assess background contamination and calculate LOD and LOQ per extraction batch, i.e. the average of blanks plus 3 and 10 times the standard deviation for blanks, for limit of detection (LoD) and limit of quantitation (LoQ), respectively. As the sample matrix can contribute to the overall background response, procedural blanks were run both before and after samples to ensure results were above detection limits and not an artefact of background variation.	Were test conditions consistent across groups? Similar sample sizes were collected for zooplankton (n=4 for each zooplankton type) and fish (n=5 for each fish).	**1**
Test organisms (if applicable)	Species: cod (15 samples) and herring (15 samples) Matrix: sludge (2 samples); stormwater (2 samples), effluent (2 samples), sediment (1 sample) Additional data, such as age of physical measurements were recorded for cod. Egg weight recorded for herrings. Health/Handling: No health observations provided.	Was the inoculum or test organism appropriate? Yes, this pelagic food web had been previously characterized and monitored for several years.	**1**

Short citation (Author, year, or ID)	**RUUS19A**		
Full citation (or link)	**Ruus A., K. Bæk, T. Rundberget, I. Allan, B. Beylich, M. Schlabach, N. Warner, K. Borgå, and M. Helberg 2019. Environmental contaminants in an urban fjord, 2018. RAPPORT L.NR. 7410-2019. Norwegian Institute for Water Research.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Government report.**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Controls	Field blanks, reference blanks, and standards were used.	Were the appropriate controls used? Yes. However, these methods and controls are not standardized, nor have they been validated.	**2**
Duration	Not relevant to study.	Was the duration of the study appropriate? Characterization of cVMS in environment included samples collected throughout 2018, not designed as a long-term monitoring study.	**-**
Methods and Observations			
Observations (half-lives, coefficients, etc.)	Data only is reported.	Were the appropriate outcomes reported? Methodology was appropriate to report outcomes of interest. The number of samples should have been clearly defined and more species should have been considered before proceeding with study.	**2**
Control performance	Control performance is reported for field blanks, only.	Was control performance acceptable? No, while multiple controls were used as QA measures (field blank, reference blank, standards), only field blank values are reported.	**2**
Sampling adequacy (frequency, duration)	Field sampling occurred during multiple periods. Herring eggs were collected in spring 2018. Sludge was collected in summer 2018, and cod collection dates are not reported.	Was the timing and frequency of sampling adequate? No, more species should have been collected and sampled for D4 given the size of the fjord system and the possible variability in D4 concentrations in field samples. This study was only conducted over multiple sampling events in 2018.	**3**
Analytical method and measurements of test substance to verify presence in test system	cVMS were analyzed by gas chromatography/mass spectrometry (GC/MS).	Were appropriate methods of analysis used? Limited or no details were provided on origin of reference materials.	**3**
Results			
Confounding variables	Contamination and volatilization are important confounding factors for D4 studies.	What sources of variability were noted, and did they affect the outcome assessment? Several measures were taken to prevent contamination during sampling and samples were processed in a clean room.	**1**
Outcomes unrelated to exposure	None mentioned.	Not applicable.	**-**
Data	No raw data was presented. Results summary:	Were the data appropriately reported to document the outcome(s)? Yes.	**1**

Short citation (Author, year, or ID)	**RUUS19A**		
Full citation (or link)	**Ruus A., K. Bæk, T. Rundberget, I. Allan, B. Beylich, M. Schlabach, N. Warner, K. Borgå, and M. Helberg 2019. Environmental contaminants in an urban fjord, 2018. RAPPORT L.NR. 7410-2019. Norwegian Institute for Water Research.**		
Study type (e.g., OECD Guideline if applicable)	**No guideline. Government report.**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**No**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	D4 tissue concentrations ranged from ND–65.79 ng/gww in cod, and D4 was not detected in herring blood or eggs. Concentrations of D4 displayed no significant relationship with trophic position		
Statistical method and kinetic calculations	Samples were extracted and analyzed in batches with a minimum of 3 procedural blanks to assess background contamination and calculate LOD and LOQ per extraction batch, i.e. the average of blanks plus 3 and 10 times the standard deviation for blanks, for LoD and LoQ, respectively. As the sample matrix can contribute to the overall background response, procedural blanks were run both before and after samples to ensure results were above detection limits and not an artefact of background variation. Oher statistical analyses are not mentioned.	Were statistics and/or kinetic calculations described and consistent? Yes.	**1**
Plausibility of results	Controls were mostly documented, but concentrations of D4 were below the limit of detection in all herring samples, which leads to uncertainty with the reported data.	Were the study results reasonable? Yes, controls provided plausibility to results. Larger sample sizes and analysis of more species may have increased likelihood of calculating detectable concentrations in D4.	**2**
		Score (18–72); without 2 criteria, possible score was 16–64:	**29**

Short citation (Author, year, or ID)	**SELCK11A**		
Full citation (or link)	**Selck, H., K. Drouillard, K. Eisenreich, A.A. Koelmans, A. Palmqvist, A. Ruus, D. Salvito, I. Schultz, R. Stewart, A. Weisbrod, A. N.W. van den Brink, and M. van den Heuvel-Greve. 2011. Explaining differences between bioaccumulation measurements in laboratory and field data through use of a probabilistic modeling approach. Integrated Environmental Assessment and Management 8(1): 42–63.**		
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
		Score (18–72):	**NA**
Note: Article is a modeling paper that compares laboratory data to field data in an attempt to understand differences in bioaccumulation measurements between these two general systems. The study does not present new data, nor does the study present any siloxane (D4, D5, etc.) data. The study used various species (insects, fish) to better define a currently used bioaccumulation model. In general, the authors report that variability in bioaccumulation assessment is reduced most by improved identification of food sources as well as by accounting for the chemical bioavailability in food components, and improvements in the accuracy of aqueous exposure appear to be less relevant when applied to moderate to highly hydrophobic compounds, because this route contributes only marginally to total uptake.			

Appendix C

Reviews of Studies on Mammalian Toxicology and Human Health Exposure

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Appendix C

Mammalian toxicology and human health exposure reviews

Short citation (Author, year, or ID)	**DOMOR17A**
Full citation (or link)	**Domoradzki, J.Y., Sushynski, C.M., Sushynski, J.M., McNett, D.A., Van Landingham, C., Plotzke, K.P. (2017) Metabolism and disposition of [^{14}C]-methylcyclosiloxanes in rats. Toxicology Letters 279 (2017) 98–114.**
Study type (e.g., OECD Guideline if applicable)	**Review of available oral toxicokinetic data in rats**
Study Director (if applicable)	**N/A**
GLP Compliance (if applicable)	**N/A**
Description: Paper is an evaluation of the available toxicokinetic data in rats and determined that data and modeling results suggest differences in metabolism between low and high dose administration indicating high dose administration results in or approaches non-linear saturated metabolism. **Remarks:** This article will be consulted during evaluation of the point of departure for risk assessment.	

Short citation (Author, year, or ID)	KRENC18A		
Full citation (or link)	Krenczkowska, D., Mojsiewicz-Pienkowska, K., Wielgomas, B., Cal, K., Bartoszewski, R., Bartoszewska, S., Jankowski, Z. (2018) The consequences of overcoming the human skin barrier by siloxanes (silicones) Part 1. Penetration and permeation depth study of cyclic methyl siloxanes. Chemosphere xxx (2018) 1-17.		
Study type (e.g., OECD Guideline if applicable)	Human in vitro dermal absorption Non-GLP Literature		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	From Sigma-Aldrich, Germany. No purity report	Was the source and purity identified?	**2**
Preparation	No, only dose level tested was 100 µL in vitro and no correlation to real-life exposure mentioned. Siloxanes were dosed in the amount of 100 µl, which corresponded to the infinite dose about 95600 µg.	Was test substance preparation described and appropriate for the test system?	**4**
Test Design			
Test model	No, model does not report % of applied dose absorbed.	Were test models reported and appropriate?	**4**
Assay procedures	No skin washing performed. Not reporting of the condition of the tissue in culture after 24 hours.	Were assay procedures appropriate?	**3**
Controls (negative, vehicle, positive)	Not applicable	Were the appropriate controls included?	**1**
Number of groups and/or replicates described	1, number of replicates is not clear	Was the number of groups and replicates appropriate?	**4**
Exposure Characterization			
Exposure consistency	Yes	Were exposures consistent across groups?	**1**
Metabolic activation (if applicable)	Not applicable	Was metabolic activation appropriate?	**1**
Exposure duration	Yes 24 hours, however washing is typical after 6-10 hours	Was the exposure duration appropriate?	**2**
Treatment groups (concentrations/doses)	100 µL (95600 µg)	Was the number of exposure groups and dose spacing appropriate?	**4**
Reporting of concentrations	Yes	Were exposure doses/concentrations reported clearly?	**1**
Methods and Observations			

Control performance	Yes - cytotoxicity (high dose levels only, skin integrity evaluation performed	Was control performance adequate?	**2**
Outcome assessment methodology	No, reports amount absorbed and not % of applied absorbed.	Was the outcome assessment methodology sensitive for the outcome(s) of interest?	**4**
Consistency of outcome assessment	Yes	Was the outcome assessment done consistently across groups?	**1**
Sampling adequacy	No, only one exposure point	Was sampling adequate for the outcomes of interest?	**4**
Blinding of assessors for subjective outcomes (if applicable)	Not reported	Were assessors of subjective outcomes blinded to treatment groups?	**4**
Confounding variables in design/procedures	Occlusion, not washing	Were there confounding differences among groups that could influence the outcome?	**3**
Results			
Outcomes unrelated to exposure	24 occlusion, lack of washing at 6-10 hours of exposure	Were there differences in study groups that were unrelated to exposure that could influence the outcome?	**4**
Data	Literature, individual data not available.	Were the data appropriately reported to document the outcomes?	**4**
Data analysis	Not able to evaluate raw data not provided.	Were statistical methods and calculations appropriate?	**4**
Data interpretation	No, using cumulative dose of the 100 ug applied 77% was absorbed. This is inconsistent with previous GLP guideline studies	Were the evaluation criteria appropriate?	**4**
Cytotoxicity	Yes but not at applied dose level	Were cytotoxicity endpoints described?	**2**
		Range of possible scores (23–92):	**64**

Short citation (Author, year, or ID)	DOBRE08A		
Full citation (or link)	Dobrev, I.D., Nong, A., Liao, K.H., Reddy M.B., Plotzke, K.P. Anderson, M.E. (2008) Assessing Kinetic Determinants for Metabolism and Oral Uptake of Octamethylcyclotetrasiloxane (D_4) from Inhalation Chamber Studies. Inhalation Toxicology, 20:361–373, 2008.		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Reliability			
Methodology	The purpose of the present study was to evaluate rate constants for saturable metabolism in the body, to estimate possible presystemic D4 clearance by respiratory-tract tissues, and to assess rate constants for uptake of D4 after oral dosing. These experiments provided the opportunity to refine current physiologically based pharmacokinetic (PBPK) models for D4 and to independently estimate key model parameters by sensitive inhalation methods.	Does the assessment use approaches that are generally accepted by the scientific community? Are assumptions described? Are calculations correct?	4
Representativeness			
Exposure scenario	Yes	Does the data closely represent exposure scenarios of interest?	1
Accessibility/Clarity			
Documentation of references	Yes	Are references provided and from quality sources?	1
Variability and Uncertainty			
Variability and uncertainty	None noted; publication therefore raw data to support not available. Methodologies and other key information on methods not provided in this document.	Does the study characterize variability and identify key uncertainties?	4
		Range of possible scores (4–16):	10

Short citation (Author, year, or ID)	**FRANZ17A**
Full citation (or link)	**Franzen, A., Greene, T., Van Landingham, C., Gentry, R. (2017) Toxicology of octamethylcyclotetrasiloxane (D_4). Toxicology Letters 279 (2017) 2–22.**
Study type (e.g., OECD Guideline if applicable)	**Review of available toxicological, mode of action and human biological relevance data**
Study Director (if applicable)	**N/A**
GLP Compliance (if applicable)	**N/A**
Description: Paper is an evaluation of the available toxicological, mode of action and biological relevance data for D4. **Remarks:** This article will be consulted during evaluation of the point of departure for risk assessment.	

Short citation (Author, year, or ID)	**IONTOX19A**		
Full citation (or link)	**IONTOX 2019. In Vitro Assessment of The Recovery of Membrane Fluidity in Rat Pituitary and Human Umbilical Vein Endothelial Cells (HUVEC), and Assessment of Vascular Endothelial Growth Factor (VEGF) Signaling in HUVEC Cells Following Exposure to Octamethylcyclotetrasiloxane (D4). Unpublished Study Number: ITX-C-040-003. IONTOX, LLC Kalamazoo, MI. December 2019.**		
Study type (e.g., OECD Guideline if applicable)	**Mechanistic** **Non-GLP**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	From Sigma-Aldrich, Germany. No purity report	Was the source and purity identified?	**2**
Preparation	D4 in 0.1% ethanol; no analytical verification of dose levels	Was test substance preparation described and appropriate for the test system?	**2**
Test Design			
Test model	Rat Pituitary and Human Umbilical Vein Endothelial Cells (HUVEC)	Were test models reported and appropriate?	**1**
Assay procedures	In this study, HUVEC cells and RC-4B/c rat pituitary cells were labeled with the fluorescent molecule DPH and exposed to the positive control SDS and 0.3%, 1%, 3%, 10% and 30% D4. Fluorescence polarization was assessed after 15 minutes exposure. In addition, cellular recovery of D4 effects on polarization were assessed by removing D4 from the cells, adding fresh culture media, and assessing polarization 15, 30, 60- and 120-minutes post-exposure. The effects of D4 on VEGF signaling in HUVEC cells was assessed. To assess whether this is a non-specific D4 effect, or a direct action of D4 on the VEGF receptor, weaned HUVEC cells were exposed to D4 in the presence and absence of sunitinib maleate, a strong inhibitor of VEGF receptor (reference?). If D4 is acting on the VEGF receptor directly,	Were assay procedures appropriate?	**1**

	sunitinib maleate + D4 exposure should result in lower ERK1/2 phosphorylation levels than D4 alone		
Controls (negative, vehicle, positive)	Yes	Were the appropriate controls included?	**1**
Number of groups and/or replicates described	Yes	Was the number of groups and replicates appropriate?	**1**
Exposure Characterization			
Exposure consistency	Yes	Were exposures consistent across groups?	**1**
Metabolic activation (if applicable)	Not applicable	Was metabolic activation appropriate?	**1**
Exposure duration	15-120 minutes	Was the exposure duration appropriate?	**1**
Treatment groups (concentrations/doses)	0, 0.3, 1, 3, 10, or 30% D4	Was the number of exposure groups and dose spacing appropriate?	**1**
Reporting of concentrations	Yes	Were exposure doses/concentrations reported clearly?	**1**
Methods and Observations			
Control performance	Yes – appropriate positive and negative controls	Was control performance adequate?	**1**
Outcome assessment methodology	Yes	Was the outcome assessment methodology sensitive for the outcome(s) of interest?	**1**
Consistency of outcome assessment	Yes	Was the outcome assessment done consistently across groups?	**1**
Sampling adequacy	Yes	Was sampling adequate for the outcomes of interest?	**1**
Blinding of assessors for subjective outcomes (if applicable)	Not reported	Were assessors of subjective outcomes blinded to treatment groups?	**4**
Confounding variables in design/procedures	None	Were there confounding differences among groups that could influence the outcome?	**1**
Results			
Outcomes unrelated to exposure	No	Were there differences in study groups that were unrelated to exposure that could influence the outcome?	**1**
Data	Yes.	Were the data appropriately reported to document the outcomes?	**1**
Data analysis	Yes	Were statistical methods and calculations appropriate?	**1**
Data interpretation	Yes	Were the evaluation criteria appropriate?	**1**
Cytotoxicity	Yes	Were cytotoxicity endpoints described?	**1**
		Range of possible scores (23–92):	**28**

Short citation (Author, year, or ID)	**KLAUN16A**
Full citation (or link)	**Klaunig, J.E., Dekant, W., Plotzke, K., Scialli, A.R. (2016) Biological relevance of decamethylcyclopentasiloxane (D5) induced rat uterine endometrial adenocarcinoma tumorigenesis: Mode of action and relevance to humans. Regulatory Toxicology and Pharmacology 74 (2016) S44-S56.**
Study type (e.g., OECD Guideline if applicable)	**Review of available toxicological mode of action and human biological relevance data**
Study Director (if applicable)	**N/A**
GLP Compliance (if applicable)	**N/A**
Description: Paper is an evaluation of the available toxicological, mode of action and biological relevance data for D4. **Remarks:** This article will be consulted during evaluation of the point of departure for risk assessment.	

Short citation (Author, year, or ID)	**IONTOX18A**		
Full citation (or link)	**IONTOX 2018. In Vitro Assessment of Fluorescence Polarization and Disruption of Pituitary Signaling in Response to Octamethylcyclotetrasiloxane (D4). Unpublished Study Number: ITX-C-040-01. IONTOX, LLC Kalamazoo, MI. December 2018.**		
Study type (e.g., OECD Guideline if applicable)	**Mechanistic** **Non-GLP**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively?	**1**
Composition (purity, origin); single substance (not mixture)	From Sigma-Aldrich, Germany. No purity report	Was the source and purity identified?	**2**
Preparation	D4 in 0.1% ethanol; 0.1% Tween-20 ro 0.1% Kolliphor; no analytical verification of dose levels	Was test substance preparation described and appropriate for the test system?	**2**
Test Design			
Test model	Rat Pituitary and immortalized pituitary cell lines	Were test models reported and appropriate?	**1**
Assay procedures	pg/mL – 1 µg/mL GnRH was added in triplicate (100 µL/well in 96-well plate) to rat primary pituitary cells. This was done for multiple exposure times (1, 4 and 24 hours). 3 – 1000 µM dopamine was added in triplicate (100 µL/well in 96-well plate) to rat primary pituitary cells. This was done for multiple exposure times (2, 6 and 24 hours). Primary pituitary cells were incubated for 24 hours (to achieve optimal prolactin release) in the presence of 30%, 10%, 3%, 1% and 0.3% D4 (with 0.1% absolute ethanol as a vehicle) or with 10%, 3%, 1%, 0.3% and 0.1% SDS. Changes in prolactin release were assessed by ELISA.	Were assay procedures appropriate?	**1**
Controls (negative, vehicle, positive)	Yes	Were the appropriate controls included?	**1**
Number of groups and/or replicates described	Yes	Was the number of groups and replicates appropriate?	**1**
Exposure Characterization			
Exposure consistency	Yes	Were exposures consistent across groups?	**1**

Metabolic activation (if applicable)	Not applicable	Was metabolic activation appropriate?	**1**
Exposure duration	1-24 hours	Was the exposure duration appropriate?	**1**
Treatment groups (concentrations/doses)	0, 0.3, 1, 3, 10, or 30% D4	Was the number of exposure groups and dose spacing appropriate?	**1**
Reporting of concentrations	Yes	Were exposure doses/concentrations reported clearly?	**1**
Methods and Observations			
Control performance	Yes – appropriate positive and negative controls	Was control performance adequate?	**1**
Outcome assessment methodology	Yes	Was the outcome assessment methodology sensitive for the outcome(s) of interest?	**1**
Consistency of outcome assessment	Yes	Was the outcome assessment done consistently across groups?	**1**
Sampling adequacy	Yes	Was sampling adequate for the outcomes of interest?	**1**
Blinding of assessors for subjective outcomes (if applicable)	Not reported	Were assessors of subjective outcomes blinded to treatment groups?	**4**
Confounding variables in design/procedures	None	Were there confounding differences among groups that could influence the outcome?	**1**
Results			
Outcomes unrelated to exposure	No	Were there differences in study groups that were unrelated to exposure that could influence the outcome?	**1**
Data	Yes.	Were the data appropriately reported to document the outcomes?	**1**
Data analysis	Not applicable	Were statistical methods and calculations appropriate?	**1**
Data interpretation	Yes	Were the evaluation criteria appropriate?	**1**
Cytotoxicity	Yes	Were cytotoxicity endpoints described?	**1**
		Range of possible scores (23–92):	**28**

Short citation (Author, year, or ID)	**DEKAN17A**
Full citation (or link)	**Dekant, W., Scialli, A.R., Plotzke, K., Klaunig, J.E. (2017) Biological relevance of effects following chronic administration of octamethylcyclotetrasiloxane (D4) in Fischer 344 rats. Toxicology Letters 279S (2017) 42–53.**
Study type (e.g., OECD Guideline if applicable)	**Review of available oral toxicokinetic data in rats**
Study Director (if applicable)	**N/A**
GLP Compliance (if applicable)	**N/A**
Description: Paper is an evaluation of toxicological effects in rats and their biological relevance to humans. **Remarks:** This article will be consulted during evaluation of the point of departure for risk assessment.	

Short citation (Author, year, or ID)	**DEKAN17C**
Full citation (or link)	**Dekant, W., Bridges, J., Scialli, A.R. (2017) A quantitative weight of evidence assessment of confidence in modes-of-action and their human relevance. Regulatory Toxicology and Pharmacology 90 (2017) 51-71.**
Study type (e.g., OECD Guideline if applicable)	**Weight of the evidence assessment include D4 impaired fertility and uterine tumors in rats**
Study Director (if applicable)	**N/A**
GLP Compliance (if applicable)	**N/A**
Description: Paper included D4 in two weight of the evidence case studies for impaired fertility and uterine tumors in rats. Also includes a review (reliability and relevance) of the mechanistic studies conducted for D4. **Remarks:** This article will be consulted during evaluation of the point of departure for risk assessment as well as during the review of the other mechanistic studies.	

Short citation (Author, year, or ID)	**GENTRY17A**		
Full citation (or link)	**Gentry, R., Franzen, A., Van Landingham, C., Greene, T., and Plotzke, K. (2017). A global human health risk assessment for octamethylcyclotetrasiloxane (D4). *Toxicology Letters, 279*: 23 – 41.**		
Study type (e.g., OECD Guideline if applicable)	**Literature; risk assessment**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Reliability			
Methodology	This human health risk assessment has been conducted to evaluate the potential hazard to workers, consumers, and the general public who may be exposed to D4 either in the workplace, through the use of consumer products containing D4,or to D4 released in the environment. Previous risk assessments and literature were reviewed. Using data from this search, the team conducted a harmonized multi-route physiologically-based pharmacokinetic (PBPK) model for both the rat and the human. Three dose-metrics were considered. The first was the external animal inhalation exposure concentration in ppm. The second was the external exposure concentrations adjusted to continuous inhalation exposure from 6 h per day for 7 days per week in the 2-generation study (Franzen et al., 2017). The third was the PBPK-derived internal dose metric (area under the curve (AUCs)) for each exposure concentration. The parent compound was assumed to be the relevant toxic moiety and the AUC of the free D4 in the blood was considered to be the relevant dose-metric for use in benchmark dose (BMD) dose-response modeling. The fit of a model to the data was determined using three different goodness-of-fit criteria: the Akaike Information Criteria (AIC), a p-value, and the scaled residual of interest (USEPA, 2015). Because of the large number of potential exposure pathways for the consumer and the general public, a Monte Carlo probabilistic analysis was conducted to prioritize those scenarios that would potentially result in the greatest exposure. Those scenarios with the largest potential exposure estimate were included in the PBPK analysis.	Does the assessment use approaches that are generally accepted by the scientific community? Are assumptions described? Are calculations correct?	**1**
Representativeness			
Exposure scenario	Though corrections using pharmacokinetic data were made, a number of studies used in the model were from animal rather than human exposure data – non-ambient. Personal care exposure not relevant to TSCA.	Does the data closely represent exposure scenarios of interest?	**2**
Accessibility/Clarity			

Documentation of references	The available toxicological literature as cited in Dekant et al.(2017), Domoradzki et al. (2017), Franzen et al. (2017), Jean and Plotzke (2017), Jean et al. (2017) as well as the studies described in other hazard assessments conducted worldwide were considered (Environmental Control Center Co. Ltd., 2011; Health Canada, 2008; REACH, 2011; REACH Registration Dossier, 2011; SCCS, 2010). The conclusions reached by Franzen et al. (2017), which is a review of the available toxicological literature for D4, were relied upon in drawing conclusions regarding the potential for hazard following exposure to D4 and to determine which endpoints were the most sensitive or were observed following exposure to the lowest concentrations.	Are references provided and from quality sources?	**1**
Variability and Uncertainty			
Variability and uncertainty	The study notes that there is a high degree of subjectivity and variability in the choice and application of uncertainty factors, not only in different countries but also in different regulatory agencies within a country (data pulled for this model assessment). Therefore, for this assessment, rather than attempting to derive factors that may be used by the various regulatory agencies worldwide to adjust the POD for low-dose extrapolation, a comparison of the internal dose metric associated with the lower bound on the benchmark dose (BMDL) to the internal dose metric estimated for each relevant exposure scenario was conducted. The use of these ratios or MOS removes the need to consider various uncertainty factors that may be applied by various regulatory agencies. To account for differences in human and rat model, potential differences in pharmacokinetics (metabolism) and pharmacodynamics (sensitivity) between the animal species and humans were considered in the estimation of human equivalent concentrations.	Does the study characterize variability and identify key uncertainties?	**1**
		Range of possible scores (4–16):	5

Short citation (Author, year, or ID)	MCMUL16A		
Full citation (or link)	**McMullin, T.S., Yang, Y., Campbell, J., Clewell, H.J., Plotzke, K., Andersen, M.E. (2016) Development of an integrated multi-species and multi-dose route PBPK model for volatile methyl siloxanes - D4 and D5. Regulatory Toxicology and Pharmacology 74 (2016) S1-S13.**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Reliability			
Methodology	Incorporation of existing PBPK models and supporting D4 kinetic studies. We used a three step process to construct a multi-compound, multi-dose route model for cVMSs that included 1) combining inhalation rodent model structures across compounds 2) coordinating model across species 3) combining routes of exposure. Table 1 shows the key model features incorporated into the current model compared to those used previously. The current computer code uses a nested algorithm to toggle specific tissues on or off depending on the chemical, the animal species and exposure route. The mass balance equations that describe the rate of change of D4 and D5 and their metabolites in various tissues are in the supplemental material (S-4). Computer code, specific scripts that reproduce all figures in this manuscript and associated documentation can be obtained from the corresponding author (TSM). The series of differential equations were solved by numerical integration using the Gear Algorithm for stiff systems in acslX version 11.8.4 (AEgis, Technologies Group, Inc, Huntsville, Alabama, USA).	Does the assessment use approaches that are generally accepted by the scientific community? Are assumptions described? Are calculations correct?	1
Representativeness			
Exposure scenario	Yes	Does the data closely represent exposure scenarios of interest?	1
Accessibility/Clarity			
Documentation of references	Yes	Are references provided and from quality sources?	1
Variability and Uncertainty			
Variability and uncertainty	Sensitivity analysis conducted and consistency of model with WHO 2010 PBPK guidelines provided a high level of confidence. In addition all background data available in supplementary data or from correspondence with authors, provided in the document Limited biomonitoring data exists	Does the study characterize variability and identify key uncertainties?	1
		Range of possible scores (4–16):	4

Short citation (Author, year, or ID)	ANDER08A		
Full citation (or link)	**Andersen, M.E., Reddy, M.B., Plotzke, K.P. (2008). Are highly lipophilic volatile compounds expected to bioaccumulate with repeated exposures. *Toxicology Letters, 179*: 85 – 92.**		
Study type (e.g., OECD Guideline if applicable)	**Pharmacokinetic analysis (PBPK model); human subjects**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Reliability			
Methodology	A generic model based on the styrene PBPK model structure (Ramsey and Andersen, 1984) was used to examine repeat inhalation exposures. Study model simulated inhalation exposures to a concentration of a VC in the ambient air, Cin. Elimination of the VC was by hepatic metabolism and by exhalation. The physiological parameters were set to appropriate values for a reference human. Although this method for estimating PCs was developed for rat tissue PCs, the PCs for rat tissue and human tissue are expected to be similar. The rat D5 PBPK model was used to simulate 6-month D5 inhalation exposures. Two modifications were made to the model. The increasing body weight of female rats was incorporated in the model by using a rectangular hyperbola equation relating body weight to time. Second, the relative size of the fat compartments increased with time. Since the starting BW was small, the total volume of the fat compartment was 5% of body weight at the beginning of the study and increased to 15% of body weight at the end of the study, 6 months later. Berkeley MadonnaTM was used to solve model equations and conduct parameter estimation by curve fitting. Berkeley Madonna code for both the generic human PBPK model and the rat inhalation model for D4 and D5 showing all equations is available from the corresponding author (MEA) upon request.	Does the assessment use approaches that are generally accepted by the scientific community? Are assumptions described? Are calculations correct? Assumption of similarity between rat and human is noted. Also noted increasing body weight of female rats in the model, and fat compartment size was modified. Data used have been used in other reports, and were obtained from previously published literature.	**2**
Representativeness			
Exposure scenario	Exposure not a part of this study; data obtained from two alternate literature studies. In those studies, Inhalation pharmacokinetics of D4 and D5 were studied in male and female Fischer 344 rats following single 6-h exposures, daily 6-h exposures for 15 consecutive days, and 6-month exposures (6-h/day, 5 days/week). The single and 15-day exposures were nose-only; the 6-month exposures were whole-body. After the exposures, the rats were sacrificed and plasma, liver and fat samples were obtained. For the single and 15-day exposures, only perirenal fat samples were obtained. For the 6-month exposure, perirenal, brown, and abdominal fat samples were obtained. The tissue samples were analyzed for D5 using	Does the data closely represent exposure scenarios of interest? Inhalation exposure not a direct part of this study, data obtained from other published research; dosing not reported in this modeling report.	**1**

	GC/MS or by liquid scintillation analysis for radioactivity (Tobin et al., 2008).		
Accessibility/Clarity			
Documentation of references	The D4 and D5 data sets used for analyses in this paper have been reported elsewhere (Plotzke et al., 2000; Tobin et al., 2008).	Are references provided and from quality sources?	**1**
Variability and Uncertainty			
Variability and uncertainty	Study notes that results fall in line with previous research, but does not identify ke4 uncertainties in the data etc.	Does the study characterize variability and identify key uncertainties?	**2**
		Range of possible scores (4–16):	**6**

Short citation (Author, year, or ID)	CAMP17A		
Full citation (or link)	Campbell Jr., J.L. Andersen, M.E., Van Landingham, C. Gentry, R., Jensend, E., Domoradzki, J.Y., Clewell III, H.J. (2017) Refinement of the oral exposure description in the cyclic siloxane PBPK model for rats and humans: Implications for exposure assessment. Toxicology Letters 279 (2017) 125–135.		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Reliability			
Methodology	The refined MC-MD PBPK model presented here expands upon this effort to include representation of rat kinetic data in plasma, tissues and exhaled breath for the parent compounds after oral bolus administration. Additional refinements were made with regards to hepatic induction of metabolism in the liver and allometric scaling of rate constants for the deep tissue compartments which will allow the MC-MD model to be used in uncertainty analysis. Overall, the refined MC-MD model was able to reproduce both parent D4 and D5 kinetic data in rat and human after inhalation exposure (rat and human) or dermal exposure (human). The inclusion of sequestered (i.e., lipid associated) oral absorption into plasma after oral bolus dosing successfully described the lack of exhalation as well as the initial distribution of siloxane to the liver which was higher than simple partitioning from plasma would allow. The refined MC-MD PBPK model presented here can be incorporated into uncertainty and variability analysis and cross-species dosimetry for both D4 and D5.	Does the assessment use approaches that are generally accepted by the scientific community? Are assumptions described? Are calculations correct?	1
Representativeness			
Exposure scenario	Yes	Does the data closely represent exposure scenarios of interest?	1
Accessibility/Clarity			
Documentation of references	Yes	Are references provided and from quality sources?	1
Variability and Uncertainty			
Variability and uncertainty	None noted; publication therefore raw data to support not available	Does the study characterize variability and identify key uncertainties?	2
		Range of possible scores (4–16):	5

Short citation (Author, year, or ID)	FROMM15A		
Full citation (or link)	**Fromme, H., Cequier, E., Kim, J.T., Hanssen, L., Hilger, B., Thomsen, C., Chang, Y.S., and Volkel, W. (2015). Persistent and emerging pollutants in the blood of German adults: Occurrence of dechloranes, polychlorinated napthalenes, and siloxanes. *Environment International*, l85: 292 - 298.**		
Study type (e.g., OECD Guideline if applicable)	Literature; human biomonitoring		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Reliability			
Sampling methodology	The Bavarian Red Cross Blood Donation Service was requested to collect blood samples of the general population on a random selection. Samples were obtained from 42 healthy blood donors living in Munich and the surrounding areas in the winter in 2013 and 2014. The blood was freshly collected by the Bavarian Red Cross Blood Donation Service. After venipuncture, each sample was centrifuged to obtain the plasma fraction and stored without preservatives at -20°C until analysis.	Did the sampling methods follow sound and widely accepted or appropriate Standard Operating Procedures?	1
Analytical methodology	The analysis was described in detail by Hanssen et al. (2013).	Did the analytical methods follow sound and widely accepted or appropriate methodology?	1
Selection of biomarker of exposure	Yes	Is the biomarker in the specified matrix highly related to exposure?	1
Representativeness			
Geographic area	Germany	Is the geographic area reported and well-described?	3
Currency	N/A	Is the timing of sampling consistent with current or recent exposures?	4
Spatial and temporal variability	N/A	Does the sampling approach accurately capture variability?	4
Exposure scenario	No exposure information available	Does the data closely represent a relevant exposure scenario (e.g., media of interest)?	4
Accessibility/Clarity			
Reporting of results	No	Are summary statistics provided or the data available to allow their calculation?	4
Quality assurance	The technical personnel wore CAT III chemical-protective coveralls, mouth guards, and powder-free nitrile gloves during the division of samples into subsamples for the different laboratories, which was conducted over a single session. On the day of sample handling, the personnel did not use any personal care products such as deodorants, hair and skin products, soaps, and cosmetics. All of the samples were prepared in a laminar flow workbench under cleanroom conditions to minimize contamination from the indoor air.	Were QA/QC measures applied and are they described?	2
Variability and Uncertainty			

Short citation (Author, year, or ID)	**FROMM15A**		
Full citation (or link)	**Fromme, H., Cequier, E., Kim, J.T., Hanssen, L., Hilger, B., Thomsen, C., Chang, Y.S., and Volkel, W. (2015). Persistent and emerging pollutants in the blood of German adults: Occurrence of dechloranes, polychlorinated napthalenes, and siloxanes. *Environment International*, l85: 292 - 298.**		
Study type (e.g., OECD Guideline if applicable)	**Literature; human biomonitoring**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Variability and uncertainty	Information of the donors are limited. Samples on a random selection, but not on a representative basis. No additional information was available about the blood donors due to the necessary limitations of data security.	Does the study characterize variability and identify key uncertainties?	4
		Range of possible scores (10-40):	28

Short citation (Author, year, or ID)	**XU12A**		
Full citation (or link)	**Xu, L., Shi, Y., Wang, T., Dong, Z., Su, W., and Cai, Y. (2012). Methyl Siloxanes in Environmental Matrices around a Siloxane Production Facility, and Their Distribution and Elimination in Plasma of Exposed Population. *Environ. Sci. Technol., 46*:11718 – 11726.**		
Study type (e.g., OECD Guideline if applicable)	**Literature; human biomonitoring in China**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Reliability			
Sampling methodology	Plasma (n = 201), air (n = 35), dust (n = 13), and soil (n = 14) samples were collected during August to October, 2011. In August 2011, 72 current workers (61 males and 11 females) from six workshops of the facility were invited to participate in the study voluntarily. In Zone B, 14 individuals (10 males and 4 females) were invited. In addition, 58 (49 males and 9 females) participants from Zone C were invited to serve as a reference group for the assessment of background siloxanes exposure in the region.	Did the sampling methods follow sound and widely accepted or appropriate Standard Operating Procedures?	1
Analytical methodology	Cyclic siloxane standards (D4, D5, D6, purity >98%), linear siloxane standards [L3, L4, polydimethylsiloxane mixture (PDMS, L5-L16, which mass profiles were shown in Supporting Information), purity > 98%)], and tetrakis (trimethylsilyoxy) silane (M4Q, purity 97%) were purchased from Sigma-Aldrich (St. Louis, MO, U.S.). Methanol, ethyl acetate, and n-hexane were purchased from Fisher Scientific (Fair Lawn, New Jersey, U.S.). Concentrations of siloxanes in both dust/soil and air samples were used to calculate the human exposure (daily intake) in the three zones. ingestion rate (Eingest, ng/day) was calculated using the following equation: IngestECdust/soil=×dustQ/soil uptake Fe. where Cdust represents the siloxane concentration in dust/soil (ng/g), and Qdust/soil represents the dust ingestion rate (g/day). A high exposure scenario based on EPA protocols was used with Qdust/soil at 0.05 g per day.22 Fuptake represents the uptake fraction of the compound. Due to the lack of directly measured specific Fuptake for siloxane, we used 1.0 as the value for all studied siloxanes. The inhalation exposure (Einhale) was calculated using the following equation: ECair=×airV×uptakFe, where Cair is the concentration of siloxanes in air (ng/m3), and Vair is the volume of inhalation (m3/day; 20 L/min for adults). As previous studies indicated that inhalation Fuptake for D4 and D5 was about 0.1 due to their low blood/air partition,16,17 our study selected 0.1 as inhalation Fuptake for cyclic compounds (D4−D6).	Did the analytical methods follow sound and widely accepted or appropriate methodology?	1

Selection of biomarker of exposure	Yes	Is the biomarker in the specified matrix highly related to exposure?	1
Representativeness			
Geographic area	The studied area is located in the east of Shandong Province, P.R. China. In this area, the predominant wind direction is southeastern between April and October, while northwestern between November and March. We divided this area into three zones (Figure 1). The siloxane production facility is located in Zone A, and has been producing cyclic and linear methyl siloxanes products for more than 15 years, with an annual yield of about 10 000 tonnes. Zone B is downwind of Zone A during April to October. In this zone, a residential community with a population of about 2000 is located about 400−1000 m from the facility. Zone C, selected as a reference zone,	Is the geographic area reported and well-described?	1
Currency	Compared against 2001 data from Germany	Is the timing of sampling consistent with current or recent exposures?	2
Spatial and temporal variability	The siloxane production facility is located in Zone A, and has been producing cyclic and linear methyl siloxanes products for more than 15 years, with an annual yield of about 10 000 tonnes. Zone B is downwind of Zone A during April to October. In this zone, a residential community with a population of about 2000 is located about 400−1000 m from the facility. Zone C, selected as a reference zone, Plasma (n = 201), air (n = 35), dust (n = 13), and soil (n = 14) samples were collected during August to October, 2011.	Does the sampling approach accurately capture variability?	1
Exposure scenario	Plasma sampling provides overall capture, but unable to distinguish between significant routes of exposure and differences in exposure route between zones	Does the data closely represent a relevant exposure scenario (e.g., media of interest)?	3
Accessibility/Clarity			
Reporting of results	No	Are summary statistics provided or the data available to allow their calculation?	4
Quality assurance	Laboratory personnel participating in this study were forbidden to use any cosmetic products; (2) No sampling or storage device during field collection was made of silica gel; (3) During GC/MS analysis (especially for cyclic methyls siloxanes), low injector port temperature (200 °C) and low-bleed capillary columns (HP-5MS) were selected to minimize siloxane bleeding from inlet septum and capillary columns; 4) During sampling events, field blanks were collected to assess potential ambient contamination. The sampling events were approved by the local municipal Center for Disease Control and Prevention (CDC), and Laiyang Central Hospital helped us to perform these events, the	Were QA/QC measures applied and are they described?	2

	institutional review board from which we also got a written consent.		
Variability and Uncertainty			
Variability and uncertainty	Despite the careful precautions, compounds D4, D5, and D6 were detected in laboratory blanks of plasma (0.06−0.3 ng/g), soil/dust (0.2−0.5 ng/g), and air samples (0.07−0.1 ng/m3), respectively. Therefore, for concentrations of D4, D5, and D6 reported in the present study, laboratory blank values have been subtracted. For these three compounds, after laboratory blank subtraction, limits of quantitation (LOQs) were determined as 10 times the standard deviation of the laboratory blank signals (n = 7). For L3−L16, which were not detectable in laboratory blanks, LOQs were determined as 10 times the standard deviation of signals of laboratory blank samples (n = 7) spiked with target compounds at low concentrations. LOQs of seventeen compounds were 0.4−1.0 ng/g for plasma, 0.5−1.0 ng/g for dust/soil, and 0.14−0.36 ng/m3 for air samples (24 h sampling), respectively. Recoveries for plasma, dust/soil, and air samples were 89−95%, 81−94%, and 86−92%, respectively. All peak areas of field blanks for plasma, dust/soil, and air samples during sampling events were less than 5% of their LOQs.	Does the study characterize variability and identify key uncertainties?	3
		Range of possible scores (10–40):	19

Short citation (Author, year, or ID)	ANONY17A		
Full citation (or link)	No author (2017) Workplace Environmental Exposure Level (WEEL) Octamethylcyclotetrasiloxane (D4). Toxicology and Industrial Health 2017, Vol. 33(1) 2–15		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Reliability			
Methodology	Derivation of the workplace environmental exposure level (WEEL®) value	Does the assessment use approaches that are generally accepted by the scientific community? Are assumptions described? Are calculations correct?	1
Representativeness			
Exposure scenario	Occupational	Does the data closely represent exposure scenarios of interest?	1
Accessibility/Clarity			
Documentation of references	Yes	Are references provided and from quality sources?	1
Variability and Uncertainty			
Variability and uncertainty	Yes	Does the study characterize variability and identify key uncertainties?	1
		Range of possible scores (4–16):	4

Short citation (Author, year, or ID)	BIEST14A		
Full citation (or link)	Biesterbos, J.W.H, Beckmann, G., Anzion,†R.B.M, Ragas, A.M.J., Russel, F.G.M., Scheepers, P.T.J. (2014) Sensitive Method for Quantification of Octamethylcyclotetrasiloxane (D4) and Decamethylcyclopentasiloxane (D5) in End-Exhaled Air by Thermal Desorption Gas Chromatography Mass Spectrometry. Anal. Chem. 2014, 86, 5794−5799.		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Reliability			
Sampling methodology	End-exhaled breath samples were collected using Bio-VOC breath samplers. The participants were instructed to inhale normally, to place the Bio-VOC breath sampler into their mouth and to exhale fully at normal speed into the sampler. Immediately following sample collection, the substances of interest were transferred to an ATD tube using the syringe (plunger). The ATD tubes were capped with Swagelock-caps and stored until analysis at ambient temperature for less than 24 h. Subsequently, 2.5 ng of 13C-labeled D4 and D5 in 0.5 µL of methanol was loaded on the ATD tubes using a loading rig (Markes International, Llantrisant, United Kingdom). The ATD tube was connected to the loading rig, the internal standard solution was injected using a syringe, and the tube was flushed with helium 5.0 (Linde Gas, Schiedam, The Netherlands) at a flow of 50 mL/min for 3 min to remove the methanol.	Did the sampling methods follow sound and widely accepted or appropriate Standard Operating Procedures?	1
Analytical methodology	The samples were analyzed by use of thermal desorption gas chromatography mass spectrometry (TD-GC-MS). The instrument consisted of a thermal desorption unit and auto sampler (Unity 2 and Ultra 2, Markes) coupled to a gas chromatograph mass spectrometer (Focus and ISQ, Thermo Scientific, Interscience Breda, The Netherlands). Electron impact ionization was used. The ATD tubes were inserted in the auto sampler and subsequently desorbed at 275 °C for 15 min, using a split flow of 10 mL/min. Samples were trapped at −10 °C by using a general purpose hydrophobic trap (U-T2GPH-2S). A 30 m Rxi-5 MS (0.25 mm i.d., 0.5 µm film thickness, Restek) was used as an analytical column. Helium 5.0 was used as carrier gas. The GC oven temperature was programmed as follows: hold for 5 min at 50 °C; 10 °C/min to 150 °C; 30 °C/min to 250 °C, hold for 2 min. The transfer line was kept at 250 °C and the ion source at 250 °C. We ran in full scan mode and the ions monitored were m/z 281 for D4, 355 for D5, 285 for 13C-labeled D4, and 360 for 13C-labeled D5, respectively. The dwell time was set at 0.4 s.	Did the analytical methods follow sound and widely accepted or appropriate methodology?	1
Selection of biomarker of exposure	Yes	Is the biomarker in the specified matrix highly related to exposure?	1
Representativeness			

Geographic area	Not reported	Is the geographic area reported and well-described?	4
Currency	Yes	Is the timing of sampling consistent with current or recent exposures?	1
Spatial and temporal variability	Yes	Does the sampling approach accurately capture variability?	1
Exposure scenario	To demonstrate the applicability of the method for quantifying values at a low range, we collected end-exhaled air samples (142 mL) in duplicate from 15 consumers exposed to PCPs (regular use) and from the same consumers after they refrained from the use of PCPs for 24 h. Regular use was described as the use of PCPs by our volunteers as they would normally do without restrictions.	Does the data closely represent a relevant exposure scenario (e.g., media of interest)?	4
Accessibility/Clarity			
Reporting of results	No raw data	Are summary statistics provided or the data available to allow their calculation?	3
Quality assurance	Several measures were taken to prevent contamination of the analytical process: (1) D4 and D5 are present in a wide variety of PCPs, such as hand creams and deodorants. All researchers, lab technicians, and instrument operators refrained from the use of these products prior to (24 h) and during the experimental and analytical work. (2) All calibration and internal standard solutions were prepared in glass jars with metal-lined screw caps to prevent contamination of the solutions due to contact with plastic (possible silicon-containing) screw caps. (3) The initial pressure regulator, regulating helium flow, was replaced by a pressure regulator with a complete iron inner lining. (4) All parts of the TD-GC-MS system that contained silicon were replaced by silicon-free alternatives (e.g., septa). Before the start of every analysis the system was checked with an empty tube, which did not contain a sorbent, to verify that the system was not a source of background contamination.	Were QA/QC measures applied and are they described?	2
Variability and Uncertainty			
Variability and uncertainty	The ubiquitous presence of cyclic siloxanes and their unique chemistry makes their analysis at trace levels challenging. Methods were included to account for background.	Does the study characterize variability and identify key uncertainties?	2
		Range of possible scores (10–40):	20

Short citation (Author, year, or ID)	HORII08A		
Full citation (or link)	Horii, Y. and Kannan, K. 2008. Survey of Organosilicone Compounds, Including Cyclic and Linear Siloxanes, in Personal-Care and Household Products. Arch Environ Contam Toxicol (2008) 55:701–710		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Reliability			
Sampling methodology	Seventy-six personal-care and household products were purchased from retail stores in Albany, New York and in Tsukuba, Japan during 2006. The samples were grouped as follows: nursing nipples (n = 4);cookware (food molds, spatulas, brushes, and cooking sheets; n = 13); sealants (caulking products; n = 3); household sanitation products (cleaners, furniture polishes, and dishwasher detergents; n = 6).	Did the sampling methods follow sound and widely accepted or appropriate Standard Operating Procedures?	2
Analytical methodology	Liquid samples were mixed thoroughly, when possible, and aliquots (0.1–0.3 g) were taken in polypropylene tubes; 500 ng of M4Q were spiked into it. Solid samples were cut into small pieces of a few square millimeters by use of solvent-cleaned scissors. Samples were weighed and shaken with 3 mL of ethyl acetate/n-hexane mixture (1:1) for 15 min and then centrifuged at 3500 rpm for 5 min. The solvent layer was transferred into another polypropylene. tube. The samples were re-extracted three times as above (12 mL in total; this is termed the first extract). After the first extraction, to confirm the extraction efficiency, the samples were soaked in 5 mL of ethyl acetate/n-hexane mixture (1:1) overnight and re-extracted by shaking for 30 min. After centrifugation, the solvent layer was transferred to another polypropylene tube (this is termed the second extract). The first and the second extracts were concentrated individually to 2–3 mL using a gentle nitrogen stream and then passed through anhydrous sodium sulfate (2 g) and a nylon filter (0.22-lm pore size, 30 mm in diameter); the rubber material was removed from syringes to avoid contamination. The final volume was set at 10 mL for the first extract and at 1 mL for the second extract, prior to GC-MS analysis. The second extraction was repeated if the target chemicals were detected at[10% of the amount measured in the first extraction. Concentrations of linear and cyclic siloxanes were determined by GC-MS (Agilent 6890GC and 5973MSD; Agilent Technologies, Foster City, CA, USA). GC separation was accomplished by use of a 30-m Rxi-5MS	Did the analytical methods follow sound and widely accepted or appropriate methodology?	1

	fused silica capillary column (0.25 mm inner diameter; 0.25 lm film thickness; Restek, Bellefonte, PA, USA). One microliter of the aliquot was injected in the splitless mode at 200C. The column oven temperature was programmed from 40C (2 min) to 220C at a rate of 20C/min and to 280C at 5C/min, which was held for 10 min (postrun at 300C for 5 min). The MS was operated in an electron impact selected ion monitoring (SIM). The ions were monitored at m/z 281 for D4.		
Selection of biomarker of exposure	Yes	Is the biomarker in the specified matrix highly related to exposure?	1
Representativeness			
Geographic area	Not applicable	Is the geographic area reported and well-described?	1
Currency	Yes, 2006	Is the timing of sampling consistent with current or recent exposures?	1
Spatial and temporal variability	Limited number of samples/sampling	Does the sampling approach accurately capture variability?	4
Exposure scenario	Not relevant - just measure of D4 in products	Does the data closely represent a relevant exposure scenario (e.g., media of interest)?	4
Accessibility/Clarity			
Reporting of results	Raw data not provided	Are summary statistics provided or the data available to allow their calculation?	4
Quality assurance	Procedural blanks (n=9) were analyzed with samples to check for contamination. The limit of quantification (LOQ) was set to be three times the levels found in procedure blanks: 351ng/g for D4.	Were QA/QC measures applied and are they described?	2
Variability and Uncertainty			
Variability and uncertainty	Limited	Does the study characterize variability and identify key uncertainties?	4
		Range of possible scores (10–40):	24

Short citation (Author, year, or ID)	TRAN15A		
Full citation (or link)	**Trans T.M, and Kannan, K. (2015) Occurrence of cyclic and linear siloxanes in indoor air from Albany, New York, USA, and its implications for inhalation exposure. Science of the Total Environment 511 (2015) 138–144.**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Reliability			
Sampling methodology	Indoor air samples were collected for 12 to 24 h by a low-volume air sampler (LP-20; A.P. Buck Inc., Orlando, FL, USA) at a flow rate of 5 L per minute. The total volume of air collected from each location ranged from 3.6 m3 to 7.2 m3. Air samples (both PUFs and filters) were kept at −18 °C until analysis. The samples were kept for no longer than 3 weeks for analysis. The samples were collected from March to May 2014 at several locations in Albany, New York, USA. The sampling locations were grouped into six categories: homes (n=20), offices (n=7), laboratories (n= 13), schools (n= 6), salons (n= 6, hair and nail salons), and public places (n= 8, e.g., shopping malls).	Did the sampling methods follow sound and widely accepted or appropriate Standard Operating Procedures?	2
Analytical methodology	The particulate samples were extracted by shaking glass fiber filters with a mixture of DCM and hexane (3:1; 20 mL; v:v) each time for 5 min, which was performed three times. The extract was concentrated in a rotary evaporator and then by a gentle stream of nitrogen to exactly 1 mL. The extract was then transferred into a GC vial. Analysis was performed on an Agilent Technologies 6890 gas chromatograph (GC) interfaced with a 5973 mass spectrometer (MS).	Did the analytical methods follow sound and widely accepted or appropriate methodology?	1
Selection of biomarker of exposure	Yes	Is the biomarker in the specified matrix highly related to exposure?	1
Representativeness			
Geographic area	Albany NY	Is the geographic area reported and well-described?	2
Currency	Yes	Is the timing of sampling consistent with current or recent exposures?	1
Spatial and temporal variability	Limited number of samples/sampling	Does the sampling approach accurately capture variability?	3
Exposure scenario	Yes	Does the data closely represent a relevant exposure scenario (e.g., media of interest)?	2
Accessibility/Clarity			

Reporting of results	Raw data not provided	Are summary statistics provided or the data available to allow their calculation?	4
Quality assurance	Efforts were taken to minimize background levels of siloxane contamination in our analysis. Procedural blanks were analyzed with every set of 8 samples. D4 levels in procedural blanks were 4.2 ± 2.46 ng.	Were QA/QC measures applied and are they described?	2
Variability and Uncertainty			
Variability and uncertainty	Limited	Does the study characterize variability and identify key uncertainties?	4
		Range of possible scores (10–40):	22

Short citation (Author, year, or ID)	YUCUI13A		
Full citation (or link)	Yucuis, R.A., Stanier, C.O., Hornbuckly, K.C. Cyclic siloxanes in air, including identification of high levels in Chicago and distinct diurnal variation. Chemosphere.2013.02.051		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Reliability			
Sampling methodology	Eight of the samples ran overnight and five samples ran during the day. The laboratory ventilation flow rate varies between 775 and 2270 cubic feet per minute depending on laboratory hood use and heating or cooling requirements.	Did the sampling methods follow sound and widely accepted or appropriate Standard Operating Procedures?	2
Analytical methodology	The extraction process involved running approximately 1.5 mL of n-hexane through the SPE cartridge directly into a GC vial. Internal standard tetrakis trimethyl-siloxysilane (M4Q, 100 ng) was then added to each vial. The samples were analyzed on a Hewlett Packard gas chromatograph mass spectrometer (HP 5973) in select ion monitoring mode. The column used was a Restek RTX-5MS. The injector temperature was 200 C. Injection volume was 2 L. The flow rate of helium gas was held at 1.0 mL/min. The temperature gradient was: 60 C (2 min), to 150 C at 10 C/min, to 300 C at 30 C/min (2 min), with a detector temperature of 250 C. The ions monitored were m/z 281 (D4 and M4Q), 355 (D5), and 341 (D6). The samples were quantified by the internal standard method. A 500 ng/mL standard containing D4, D5, D6, and M4Q was used to calculate the relative response factors for each run.	Did the analytical methods follow sound and widely accepted or appropriate methodology?	1
Selection of biomarker of exposure	Yes	Is the biomarker in the specified matrix highly related to exposure?	1
Representativeness			
Geographic area	Indoor samples were collected in the Seamans Center for the Engineering Arts and Sciences at the University of Iowa: ten samples in one laboratory, one in a student office (Office A), and three in a second office (Office B). Both offices are used during regular daytime work hours (between 9 am and 5 pm) by up to ten people. The laboratory has between one and seven occupants during daytime hours. Two outdoor locations in Iowa were chosen as representative of medium and low population density sites. The rural site is approximately three miles north	Is the geographic area reported and well-described?	2

	of West Branch, IA (population 2400) at the base of a NOAA tall tower for carbon cycle gas sampling (Andrews et al., 2013). The mid-sized city selected for the transition site was Cedar Rapids, IA (population 122000) at the Linn County Public Health Department's air quality monitoring station. The urban samples were taken at the EPA's Integrated Atmospheric Deposition Network (IADN) site at the Illinois Institute of Technology (IIT) campus in Chicago.		
Currency	Yes	Is the timing of sampling consistent with current or recent exposures?	1
Spatial and temporal variability	Limited number of samples/sampling	Does the sampling approach accurately capture variability?	3
Exposure scenario	Yes	Does the data closely represent a relevant exposure scenario (e.g., media of interest)?	2
Accessibility/Clarity			
Reporting of results	Raw data not provided; supplementary data available	Are summary statistics provided or the data available to allow their calculation?	3
Quality assurance	The overall average field blank mass for indoor and outdoor air was 3.2 ng per cartridge for D4. A field blank concentration was determined by dividing the mass of the field blanks for each site by the average volume sampled at each site. A specific limit of detection (LOD) and limit of quantification (LOQ) was then calculated for each combination of site and compound. The LOD was determined by the average of the field blank concentration plus three times the standard deviation, and the LOQ is the average plus ten times the standard deviation. Duplicate samples exhibit an average relative percent difference of 13% for 34 sample pairs. The results were not blank corrected. No corrections were made for storage, although authors recognize that some D4 may be present due to transformation after sampling.	Were QA/QC measures applied and are they described?	3
Variability and Uncertainty			
Variability and uncertainty	Limited	Does the study characterize variability and identify key uncertainties?	4
		Range of possible scores (10–40):	22
Short citation (Author, year, or ID)	**ZHANG12A**		

Full citation (or link)	Zhang, K, Wong, J.W., Begley, T.H., Hayward, D.G., Limm, W. 2012. Determination of siloxanes in silicone products and potential migration to milk, formula and liquid simulants. Food Additives and Contaminants 2012, I-11		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Reliability			
Sampling methodology	Silicone nipples and silicone bakewares were extracted using pressurized solvent extraction (PSE) and analyzed using the GC- MS-SIM method. In total, 22 products were analyzed for the six siloxanes, including three food grade silicone fluids, eight silicone bakewares and 11 silicone nipples.	Did the sampling methods follow sound and widely accepted or appropriate Standard Operating Procedures?	2
Analytical methodology	A pressurized solvent extraction procedure coupled with a gas chromatography-mass spectrometry-selective ion monitoring (GC- MS-SIM) method was developed to determine the presence of D4 in silicon products. Additionally, two different extraction methods were developed to measure these siloxanes migrating into milk, infant formula and liquid simulants (SO and 95% ethanol in water).	Did the analytical methods follow sound and widely accepted or appropriate methodology?	3
Selection of biomarker of exposure	Yes	Is the biomarker in the specified matrix highly related to exposure?	3
Representativeness			
Geographic area	Not applicable	Is the geographic area reported and well-described?	2
Currency	Yes	Is the timing of sampling consistent with current or recent exposures?	1
Spatial and temporal variability	Limited number of samples/sampling	Does the sampling approach accurately capture variability?	3
Exposure scenario	Yes	Does the data closely represent a relevant exposure scenario (e.g., media of interest)?	3
Accessibility/Clarity			
Reporting of results	Raw data not provided	Are summary statistics provided or the data available to allow their calculation?	4
Quality assurance	Not detailed	Were QA/QC measures applied and are they described?	4
Variability and Uncertainty			
Variability and uncertainty	Limited	Does the study characterize variability and identify key uncertainties?	4
		Range of possible scores (10–40):	29

Short citation (Author, year, or ID)	**WANG13B**
Full citation (or link)	**Wang, D.G., H. Steer, T. Tait, Z. Williams, G. Pacepavicius, T. Young, T. Ng, S.A. Smyth, L. Kinsman, and M. Alaee. 2013. Concentrations of cyclic volatile methylsiloxanes in biosolid amended soil, influent, effluent, receiving water, and sediment of wastewater treatment plants in Canada. Chemosphere 93(5): 766-773.**
Study type (e.g., OECD Guideline if applicable)	**Literature**
Study Director (if applicable)	**N/A**
GLP Compliance (if applicable)	**N/A**
Description: Paper discusses a program that assessed the fate of cVMSs in environmental compartments impacted by wastewater effluent discharges to understand the environmental exposure to cVMSs. A newly developed method was used to quantify cVMSs. **Remarks:** This article will be consulted during evaluation human exposure to biosolid-amended agriculture.	

Appendix D

Reviews of Studies on Ecological Hazards

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Appendix D

Reviews are presented in the order found in Table 6-8 in the main text.

The following studies were reviewed by other authoritative sources and thus are not included in this appendix: SPRIN90D, FIRMI84A, SPRIN90B, SPRIN90F, SPRIN90A, SPRIN90E, SPRIN91C, SPRIN90C, KENT94A, SPRIN91A, SPRIN91B.

Ecotoxicological reviews

Short citation (Author, year, or ID)	**DOWCO92A**		
Full citation (or link)	**Dow Corning Corporation. 1992. An 18-day aquatic toxicity test of octamethylcyclotetrasiloxane in rainbow trout of different size under flow-through saturated conditions. Report no.: 1992-I0000-37078. April 8.**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**R. B. Annelin**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score***
Test Substance			
Identity	D4	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	Purity: >99.9% Origin: Dow Corning	Was the source and purity identified? Yes	**1**
Preparation	Dechlorinated municipal water was saturated with 15 g of D4 in connected glass vessels and was gently stirred. A tube was used to transfer water from the bottom of one glass vessel into the next vessel. This solution was used as the stock solution.	Was test substance preparation described and appropriate for the test system? No lid was used to minimize volatilization. Measured levels of D4 used in test water are provided in table II. However, details were not provided on how the final water concentration of D4 was prepared, or amount of water used to make the stock test solution.	**2**
Test Design			
Test system (field, lab, static, flow-through, open/closed, etc.)	A closed system with a modified constant flow serial diluter was used in the laboratory. A minimal flow condition was used to maintain dissolved oxygen (approximately 12 mL/min).	Was the test system appropriate for the test substance and desired outcome(s)? Yes, the test system was closed.	**1**

Short citation (Author, year, or ID)	**DOWCO92A**		
Full citation (or link)	**Dow Corning Corporation. 1992. An 18-day aquatic toxicity test of octamethylcyclotetrasiloxane in rainbow trout of different size under flow-through saturated conditions. Report no.: 1992-I0000-37078. April 8.**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**R. B. Annelin**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score***
	Flow through in the system occurred for at least 243 hours prior to test initiation.		
Test conditions (test vessels, pH, temperature, media, etc.)	Fish were contained in 1.7 L glass gas-drying columns that were partially submerged in a water bath. Control water and prepared text water were added to the test system using tubes. The system used was closed (sealed).	Were the test conditions appropriate? Yes, however no details were provided on test conditions such as water temperature, pH, dissolved oxygen, or lighting conditions. Though water quality results were provided, it is not clear the accepted range of conditions that were appropriate for the test.	**2**
Test organisms (species, age, health, handling)	Species: Rainbow trout (*Oncorhynchus mykiss*) Size for Exposure 1: 4 cm in length; 1 g in weight Size for Exposure 2: 7 cm in length; 5 g in weight	Was the test species, age, etc. appropriate? Yes	**1**
Test organism acclimation	Organisms monitored for 6 days prior to exposures for mortality, disease, and other abnormal occurrences. Culture water during acclimation was the same as stock water used for exposures, and was maintained under same conditions used in the test system. Fish were fed a commercial diet during acclimation and during the exposure except when fasting. Fish underwent a fasting period of 48 hours prior to test initiation and during the first 48 hours of the test.	Were test organisms acclimated appropriately? Yes, however culture conditions such as water temperature, pH, and dissolved oxygen content were not provided.	**2**
Controls (negative, vehicle, positive)	Control vessels used with culture water and a solvent internal standard was used during GC analysis.	Were the appropriate controls used? Yes	**1**
Number of organisms and replicates per group	Exposure 1 (1g fish): 10 fish/vessel 2 control vessels, 2 exposure vessels Exposure 2 (5 g fish): 5 fish/vessel 2 control vessels, 2 exposure vessels	Was the number of organisms and replicates per group appropriate? Yes, however more vessel replicates could have been used and the same amount of fish for each exposure.	**2**
Number of exposure groups and spacing	One exposure per fish size group Exposure 1: 18 days at 23 ± 8 ppb (equivalent to 0.023 mg/L) Exposure 2: 18 days at 31 ± 10.2 ppb (equivalent to 0.031 mg/L)	Were the number of exposure groups and spacing between them appropriate? No details provided on why exposure levels were chosen. More exposure levels could have been tested.	**4**

Short citation (Author, year, or ID)	**DOWCO92A**		
Full citation (or link)	**Dow Corning Corporation. 1992. An 18-day aquatic toxicity test of octamethylcyclotetrasiloxane in rainbow trout of different size under flow-through saturated conditions. Report no.: 1992-I0000-37078. April 8.**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**R. B. Annelin**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score***
Randomized design	No details provided.	Were organisms randomly allocated to groups? No, no details are given.	**4**
Exposure Characterization			
Testing at or below solubility	23 ± 8 ppb (equivalent to 0.023 mg/L) in initial exposure and 31 ± 10 ppb (equivalent to 0.031 mg/L). Exposures began with water samples at or above water solubility, but levels rapidly decreased to half the water solubility level during the duration of the tests.	Were exposure concentrations at or below the water solubility limit? Yes, assumed to be at the solubility limit. Was the solvent concentration appropriate? No solvent was used.	**2**
Exposure consistency	Organism exposure was not consistent among the two exposures. There was only one test concentration per fish size group.	Were exposures consistent across groups? Within exposure groups testing was consistent, but organism exposure was not consistent between the two exposures. For the 1 g organisms used in Exposure 1, the D4 exposure was 23.2 ± 8 mg/L and was 31.2 ± 10 mg/L for the 5 g fish used in Exposure 2 (mean and standard deviation). One test concentration is not appropriate for toxicity testing.	**4**
Exposure route and method (aqueous, via soil, etc.)	Aqueous exposure. D4 was mixed with municipal water and then diluted once in the test chamber. Toxicity was not the objective of the study, bioconcentration was.	Was the exposure route and method appropriate? Yes, for bioconcentration testing, but it was not appropriate for determining toxicity.	**3**
Exposure period (length, dosing frequency)	Exposure duration: 18 days Dosing frequency: continuous flow-through	Was the exposure frequency and duration appropriate? Yes	**1**
Treatment groups (concentrations/doses/rates)	The number of treatments was 2; one treatment per fish size group. A range of concentrations were not used to determine levels at which toxicity would be observed No spacing of doses was used.	Was the number of groups and spacing of doses appropriate? No, single treatment is not appropriate for toxicity testing.	**4**

Short citation (Author, year, or ID)	**DOWCO92A**		
Full citation (or link)	**Dow Corning Corporation. 1992. An 18-day aquatic toxicity test of octamethylcyclotetrasiloxane in rainbow trout of different size under flow-through saturated conditions. Report no.: 1992-I0000-37078. April 8.**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**R. B. Annelin**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score***
Measurement of test substance concentration	GC analysis of whole body fish samples and test water. Internal standard of dodecamethylpentasiloxane for GC analysis. Deceased fish were removed during the exposure and all surviving fish at the test termination were analyzed for D4 content using solvent extraction and GC analysis.	Were test substance concentrations measured if poorly water soluble? GC is an appropriate method for quantifying D4. However, no details on recoverability of methods. No data presented on recoverability of internal standard.	**2**
Methods and Observations			
Control organism performance	100% survival in control vessels for both exposure.	Were the biological responses of the negative control group adequate? Yes	**1**
Outcome assessment methodology	Fish were observed every day for mortality and other effects such as non-specific narcosis (dark integument or loss of equilibrium). Weight at test termination was measured and bioconcentration factor (BCF) was determined.	Was the outcome assessment methodology sensitive for the outcome(s) of interest? Yes, for bioconcentration testing; No, for toxicity testing.	**4**
Consistency of outcome assessment	No inconsistencies in the execution of study methods or reporting of results were noted.	Was the outcome assessment done consistently across treatment groups? o for toxicity testing, there was only one treatment group.	**4**
Sampling adequacy	Yes, daily measurements of mortality were conducted, but there was little replication and only one test concentration per fish size group. Water chemistry analysis included dissolved oxygen levels and pH in exposure and control vessels at start, termination, and every Monday, Wednesday, and Friday. Analyses also included D4 levels in water.	Was sampling adequate for the outcome(s) of interest? Yes, for bioconcentration testing; no, for toxicity testing In addition, no details presented on daily concentrations of D4 in the exposure vessels was provided.	**4**
Confounding variables in design/procedures	No confounding variables noted.	Were there confounding differences among groups that could influence the outcome? No	**1**
Results			
Data	Tables of raw data were reported. <u>Results summary:</u>	Were the data appropriately reported to document the outcome? No, for toxicity testing. While no mortality was observed, only one concentration per fish size group was used. Yes,	**4**

Short citation (Author, year, or ID)	**DOWCO92A**		
Full citation (or link)	**Dow Corning Corporation. 1992. An 18-day aquatic toxicity test of octamethylcyclotetrasiloxane in rainbow trout of different size under flow-through saturated conditions. Report no.: 1992-I0000-37078. April 8.**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**R. B. Annelin**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score***
	4 cm (apr. 1 g) trout: Mortality began on day 5 and an 80% mortality at end of test. Fish showed non-specific narcosis. Mean D4 level in deceased fish was 106 mg/kg wet weight and in surviving fish 316 mg/kg wet weight. 7 cm (apr. 5 g) trout: no mortality but possible weight loss. Bioconcentration factor (BCF) after 18 days in live fish was 5,000 – 15,000, though may not be representative of steady-state conditions. Concluded that D4 at 23 ppb (equivalent to 0.023 mg/L) after 18 days causes mortality in fish weighing 1 g though mortality was not observed in fish weighing >3 g. Thus, the 18-day NOEC for 7 cm fish = 31.2 Mortality results for the 1 g and 5 g fish were presented for each day and no mortality occurred at 96 hours; thus, the 96-hr NOEC ≥23 µg/L and the 96-hr LC50 ≥23.2 µg/L for both the 1 g and 5 g fish.	for bioconcentration testing; however, the exposures were not conducted in steady-state. The D4 exposures began with D4 concentrations at or near water solubility levels and levels rapidly decreased to half the known water solubility for the duration of the exposures.	
Outcome unrelated to exposure	No biological outcomes unrelated to exposure (e.g., infections) were noted.	Were there differences in study groups that were unrelated to exposure that could influence the outcome? No	**1**
Statistical methods	No details on statistical methods were provided.	Were statistical methods appropriate? No	**4**
Estimate of variability	No variability issues were mentioned.	Were unexpected outcomes explained and variability discussed? not applicable	**1**
		Range of possible score (26–104):	**61**

Notes:

*The scores for this study are based on the toxicity endpoint, not the bioconcentration endpoint.

Short citation (Author, year, or ID)	**DOWCO08A**		
Full citation (or link)	**Dow Corning Corporation. 2008. 14C-Octamethylcyclotetrasiloxane (14C-D4): Prolonged Toxicity to the Rainbow Trout (*Oncorhynchus mykiss*) Under Flow-Through Test Conditions. HES Study No.: 10988-101. Report Number: 2008-I0000-59686.**		
Study type (e.g., OECD Guideline if applicable)	**OECD Guideline 204, Fish, Prolonged Toxicity Test: 14-day Study**		
Study Director (if applicable)	**Drottar, K.R.**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	14C-Octamethylcyclotetrasiloxane (14C-D4)	Was the test substance identified definitively? Yes.	**1**
Composition (purity, origin); single substance (not mixture)	Radiochemical purity=99.3±.006% Origin: Dow Corning Corp, Auburn, MI Single substance: Yes	Was the source and purity identified? Yes, the source and lot number were provided.	**1**
Preparation	A primary stock of 14C-D4 was prepared by quantitatively transferring 0.562 g of 14C-D4 to a 1000-mL volumetric flask using dimethylformamide (DMF). The flask was then brought to volume with DMF and mixed; this was the primary stock for further dilutions. The concentration of the primary stock was measured by liquid scintillation counting.	Was test substance preparation described and appropriate for the test system? Yes.	**1**
Test Design			
Test system (field, lab, static, flow-through, open/closed, etc.)	Lab, flow-through, open system. Continuous-flow diluter with flow rates adjusted to provide 7.2 volume additions per day to each test vessel. Diluter equilibrated 3 days prior to test initiation and checked twice daily during the exposure.	Was the test system appropriate for the test substance and desired outcome(s)? For highly volatile substances, such as D4, a closed system with minimal headspace is best; this system was open. However, chemical concentrations were measured daily and used to characterize exposure.	**2**
Test conditions (test vessels, pH, temperature, media, etc.)	Vessel: 25-L polyethylene aquaria of 15-L of test solution covered with plexiglass to prevent fish escape Temperature 11.5 to 12.5ºC. pH: 7.3 to 7.7 Dissolved oxygen: ≥7.6 mg/L Medium: The dilution water was dechlorinated municipal tap water Lighting: 16 hrs light : 8 hrs dark Loading rate of organisms = 0.011 g of fish/L of water/24 hours	Were the test conditions appropriate? Yes. However polyethylene is not typically used for test chambers if the test material has a tendency to sorb to organic substances.	**2**
Test organisms (species, age, health, handling)	Species: Rainbow trout (*Oncorhynchus mykiss*) Age: juvenile (average= 26mm, 0.12 g) Health/Handling: Pre-test mortality was 1%	Was the test species, age, etc. appropriate? Yes.	**1**

Short citation (Author, year, or ID)	**DOWCO08A**		
Full citation (or link)	**Dow Corning Corporation. 2008. 14C-Octamethylcyclotetrasiloxane (14C-D4): Prolonged Toxicity to the Rainbow Trout *(Oncorhynchus mykiss)* Under Flow-Through Test Conditions. HES Study No.: 10988-101. Report Number: 2008-I0000-59686.**		
Study type (e.g., OECD Guideline if applicable)	**OECD Guideline 204, Fish, Prolonged Toxicity Test: 14-day Study**		
Study Director (if applicable)	**Drottar, K.R.**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test organism acclimation	Duration: 19 days in dilution water as used in the test at the same temperature as used in study. Temperature: 11.3 to 13.7ºC.	Were test organisms acclimated appropriately? Yes.	**1**
Controls (negative, vehicle, positive)	Negative (dilution water) control and solvent control (0.1 mL/L DMF) were used	Were the appropriate controls used? Yes.	**1**
Number of organisms and replicates per group	10 organisms/vessel 2 replicates/group	Was the number of organisms and replicates per group appropriate? Yes.	**1**
Number of exposure groups and spacing	5 groups: 3.5, 7.0, 14, 28, and 56 µg/L (nominal); mean measured concentrations were 1.9, 3.4, 6.8, 13 and 29 µg/L	Were the number of exposure groups and spacing between them appropriate? Yes.	**1**
Randomized design	Organisms were randomly assigned to test vessels at test initiation	Were organisms randomly allocated to groups? Yes.	**1**
Exposure Characterization			
Testing at or below solubility	Only the highest test concentration was at the functional solubility limit; the remaining four test concentrations were below the solubility limit.	Were exposure concentrations at or below the water solubility limit? Yes. Was the solvent concentration appropriate? Yes, (0.1 mL/L) and no mortality was observed in the solvent control.	**1**
Exposure consistency	Three times during the test a stock solution delivery pump stalled. Additional samples were collected as necessary to document the exposure concentrations. When all samples collected during the test were averaged, the mean measured concentrations were 1.9, 3.4, 6.8, 13 and 29 µg/L; which represented 54, 49, 49, 46 and 52% of nominal, respectively.	Were exposures consistent across groups? Because the system was open, which could lead to D4 volatilization, and the pump stalled three times during the study, the exposure was not likely to be as consistent as expected for ideal circumstances. Day 4 chemistry showed lower concentrations than the other measurement days.	**3**
Exposure route and method (aqueous, via soil, etc.)	Aqueous exposure. D4 was mixed with solvent and then made into test dilutions using a continuous-flow diluter system	Was the exposure route and method appropriate? Yes.	**1**
Exposure period (length, dosing frequency)	Exposure duration: 14 days Dosing frequency: Continuous flow-through	Was the exposure frequency and duration appropriate? Yes.	**1**
Treatment groups (concentrations/doses/rates)	The number of treatments was five.	Was the number of groups and spacing of doses appropriate? Yes.	**1**

Short citation (Author, year, or ID)	DOWCO08A		
Full citation (or link)	Dow Corning Corporation. 2008. 14C-Octamethylcyclotetrasiloxane (14C-D4): Prolonged Toxicity to the Rainbow Trout (*Oncorhynchus mykiss*) Under Flow-Through Test Conditions. HES Study No.: 10988-101. Report Number: 2008-I0000-59686.		
Study type (e.g., OECD Guideline if applicable)	OECD Guideline 204, Fish, Prolonged Toxicity Test: 14-day Study		
Study Director (if applicable)	Drottar, K.R.		
GLP Compliance (if applicable)	Y		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	The spacing of doses was a factor of 2.		
Measurement of test substance concentration	Chemical measurements were made daily in each replicate. Pre-test measurements of D4 had recoveries that ranged from 47 to 58% of nominal concentrations. Analyses done by liquid scintillation counting. However, documentation of recovery and repeatability data were not provided. Samples from the highest treatment group on days 0, 7 and 14 were also analyzed by HPLC/RAM and indicated ≥ 93% of the radioactivity was parent D4.	Were test substance concentrations measured if poorly water soluble? Yes, but recovery and repeatability data were not reported.	**2**
Methods and Observations			
Control organism performance	Negative control had 5% cumulative mortality; solvent control had 0% mortality	Were the biological responses of the negative control group adequate? Yes, was ≤ 10%..	**1**
Outcome assessment methodology	The outcome assessment included daily observations of mortality and clinical signs of toxicity or abnormal behavior. Total length and wet weight were measured in all remaining fish at test termination.	Was the outcome assessment methodology sensitive for the outcome(s) of interest? Yes.	**1**
Consistency of outcome assessment	No inconsistencies in the execution of study methods or reporting of results were noted.	Was the outcome assessment done consistently across treatment groups? Yes.	**1**
Sampling adequacy	Yes, measurements of mortality and chemical concentrations were done daily.	Was sampling adequate for the outcome(s) of interest? Yes.	**1**
Confounding variables in design/procedures	No confounding variables noted.	Were there confounding differences among groups that could influence the outcome? No	**1**
Results			
Data	Tables of raw data were reported. Results summary: The 96-hr LC50 was >29 µg/L, and 96-hr LC05 was 29 µg/L. The 14-day LC50 was 17 µg/L with 95% confidence limits of 14 and 21 µg/L. The NOEC was 6.8 µg/L and the LOEC was 13 µg/L based on mortality; length and weight were not affected at concentrations ≤ 6.8 µg/L.	Were the data appropriately reported to document the outcome? Yes.	**1**

Short citation (Author, year, or ID)	**DOWCO08A**		
Full citation (or link)	**Dow Corning Corporation. 2008. 14C-Octamethylcyclotetrasiloxane (14C-D4): Prolonged Toxicity to the Rainbow Trout (*Oncorhynchus mykiss*) Under Flow-Through Test Conditions. HES Study No.: 10988-101. Report Number: 2008-I0000-59686.**		
Study type (e.g., OECD Guideline if applicable)	**OECD Guideline 204, Fish, Prolonged Toxicity Test: 14-day Study**		
Study Director (if applicable)	**Drottar, K.R.**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Outcome unrelated to exposure	No biological outcomes unrelated to exposure (e.g., infections) were noted.	Were there differences in study groups that were unrelated to exposure that could influence the outcome? No.	**1**
Statistical methods	Probit analysis was used for LC50 determination. NOEC/LOEC was determined by Fisher's Exact Test (comparison to pooled controls)	Were statistical methods appropriate? Yes.	**1**
Estimate of variability	Unexpected variability in chemical measurements were discussed and explained. Mean concentrations of chemical concentrations were used.	Were unexpected outcomes explained and variability discussed? Yes, the unexpected pump stalls led to lower concentrations on Day 4 of the experiment. The open system also likely led to volatilization, which was supported by the mean measured concentrations representing 46-54% of the nominal concentrations.	**2**
		Score (26–104):	**32**

Short citation (Author, year, or ID)	**SPRIN91E**		
Full citation (or link)	**Springborn Laboratories, Inc. 1991e. Bioconcentration and Elimination of ^{14}C-residues by Fathead Minnows (*Pimephales promelas*) Exposed to Octamethylcyclotetrasiloxane. Supplemental Study. Report 91-6-3809; Springborn Laboratories, Inc. Wareham, MA. 70 pp.**		
Study type (e.g., OECD Guideline if applicable)	**EPA 797.1520**		
Study Director (if applicable)	**P.H. Fackler, Ph.D.**		
GLP Compliance (if applicable)	**Yes**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score***
Test Substance			
Identity	^{14}C-octamethylcyclotetrasiloxane (OMCTS)	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	>98% purity, Sigma Chemical Company; not a mixture	Was the source and purity identified? Yes	**1**
Preparation	Radiolabeled D4 was dissolved in 25 mL of acetone	Was test substance preparation described and appropriate for the test system? Yes	**1**
Test Design			
Test system (field, lab, static, flow-through, open/closed, etc.)	Flow-through, sealed system, no headspace. Test vessels were 50 L spherical glass reaction flasks with glass covers and three ports that were sealed..	Was the test system appropriate for the test substance and desired outcome(s)? Yes	**1**
Test conditions (test vessels, pH, temperature, media, etc.)	Dissolved oxygen was above 8 mg/L, temperature was 21 to 22ºC, and pH was near neutral (7.0-7.6)	Were the test conditions appropriate? Yes	**1**
Test organisms (species, age, health, handling)	Fathead minnows (*Pimphales promelas*), ≤6 months of age and immature	Was the test species, age, etc. appropriate? Yes	**1**
Test organism acclimation	Test fish were acclimated for a minimum of 14 days prior to testing	Were test organisms acclimated appropriately? Yes	**1**
Controls (negative, vehicle, positive)	Solvent (acetone) control, 3.3 µL/L	Were the appropriate controls used? Yes, for bioconcentration testing, but a dilution water control should also have been used for toxicity.	**2**
Number of organisms and replicates per group	70 fish per test vessel (two with D4: “treatment” and “metabolism”) and one solvent control. Loading of fish 0.07 g/L of the 24-h flow-through volume	Was the number of organisms and replicates per group appropriate? No replicates were used.	**2**
Number of exposure groups and spacing	One group was tested, which is appropriate for bioconcentration testing, but not appropriate for toxicity testing.	Were the number of exposure groups and spacing between them appropriate? Yes, for bioconcentration testing. No, not for toxicity testing.	**4**
Randomized design	No mention that organisms were randomly allocated to replicates.	Were organisms randomly allocated to groups? Unknown.	**4**
Exposure Characterization			

Short citation (Author, year, or ID)	**SPRIN91E**		
Full citation (or link)	**Springborn Laboratories, Inc. 1991e. Bioconcentration and Elimination of ^{14}C-residues by Fathead Minnows (*Pimephales promelas*) Exposed to Octamethylcyclotetrasiloxane. Supplemental Study. Report 91-6-3809; Springborn Laboratories, Inc. Wareham, MA. 70 pp.**		
Study type (e.g., OECD Guideline if applicable)	**EPA 797.1520**		
Study Director (if applicable)	**P.H. Fackler, Ph.D.**		
GLP Compliance (if applicable)	**Yes**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score***
Testing at or below solubility	The report states that testing was conducted at water solubility without using a saturation system. The test concentration 0.5 µg/L (nominal concentration) is extremely low.	Were exposure concentrations at or below the water solubility limit? Yes. Was the solvent concentration appropriate? Yes.	**1**
Exposure consistency	There was only one test group.	Were exposures consistent across groups? No, not for toxicity testing.	**4**
Exposure route and method (aqueous, via soil, etc.)	Aqueous exposure with radiolabeled D4. A saturation system was not needed because very low concentration 0.5 µg/L (nominal concentration) was used. Toxicity was not the objective of the study, bioconcentration was.	Was the exposure route and method appropriate? Yes, for bioconcentration testing, but it was not appropriate for determining toxicity.	**3**
Exposure period (length, dosing frequency)	28 days, flow-through	Was the exposure frequency and duration appropriate? Yes	**1**
Treatment groups (concentrations/doses/rates)	0.5 µg/L nominal concentration; 0.26 µg/L was mean measured concentration in the exposure vessel. The system delivered 1.15 µL/min of chemical stock solution or acetone (solvent control) for the exposure vessel. During depuration, 350 mL/min of untreated dilution water flowed into the test vessels.	Was the number of groups and spacing of doses appropriate? Number of treatments was 1 and spacing of doses does not apply. Single treatment is not appropriate for toxicity testing.	**4**
Measurement of test substance concentration	Radioactivity was measured by liquid scintillation spectrometer. ^{14}C-residues in the water of the test vessels were monitored daily during the exposure phase (14 days) and on days 1, 3, 7, 10, 12, and 14 of the depuration phase. Samples on day 27 of exposure were analyzed by HPLC. ^{14}C-residues in whole body tissue of fathead minnows were measured in four fish collected and analyzed from the treatment vessel on days 1, 3, 7, 10, 14, 18, 22, and 28 of exposure and days 1, 3, 7, 12, and 14 of depuration. Fish from the metabolism vessel were removed after 28 days of exposure, dissected, and analyzed by HPLC after combustion and extraction.	Were test substance concentrations measured if poorly water soluble? Yes.	**1**
Methods and Observations			

Short citation (Author, year, or ID)	**SPRIN91E**		
Full citation (or link)	**Springborn Laboratories, Inc. 1991e. Bioconcentration and Elimination of ^{14}C-residues by Fathead Minnows (*Pimephales promelas*) Exposed to Octamethylcyclotetrasiloxane. Supplemental Study. Report 91-6-3809; Springborn Laboratories, Inc. Wareham, MA. 70 pp.**		
Study type (e.g., OECD Guideline if applicable)	**EPA 797.1520**		
Study Director (if applicable)	**P.H. Fackler, Ph.D.**		
GLP Compliance (if applicable)	**Yes**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score***
Control organism performance	Toxicity in solvent control: not stated Bioconcentration in solvent control: all measured water concentrations were non detect (<0.0865-<0.0874 µg/L); all measured fish tissues were non detect (<0.669-<1.28 µg/kg) (Table 5)	Were the biological responses of the negative control group adequate? No for toxicity testing, yes for bioconcentration testing.	**4**
Outcome assessment methodology	Bioconcentration factors were determined.	Was the outcome assessment methodology sensitive for the outcome(s) of interest? Yes, for bioconcentration testing; No, for toxicity testing.	**4**
Consistency of outcome assessment	There was only one treatment group.	Was the outcome assessment done consistently across treatment groups? No for toxicity testing, there was only one treatment group.	**4**
Sampling adequacy	Not appropriate for toxicity. Yes, the number of water and fish for bioconcentration was appropriate.	Was sampling adequate for the outcome(s) of interest? Yes, for bioconcentration testing; no, for toxicity testing	**4**
Confounding variables in design/procedures	No confounding factors.	Were there confounding differences among groups that could influence the outcome? No	**1**
Results			
Data	No mortality occurred in the exposure (14 days) and depuration (14 days) periods. The measured test concentration in the exposure vessel was 0.26 µg/L. Steady state was reached on Day 7. The bioconcentration factor (BCF) was determined by dividing the mean measured equilibrium ^{14}C-residue tissue concentration (2826 µg/kg, days 7-28) by the mean measured test solution concentration during the same period (0.23 µg/L, days 7-28) and that value was 12,400. Following 14 days of depuration, an average of 45% of the accumulated ^{14}C-residues remained in the tissues of exposed fish. Both carcass and viscera showed to only contain 14C-D4, with no evidence of metabolism.	Were the data appropriately reported to document the outcome? Yes, for bioconcentration testing. No, for toxicity testing. While no mortality was observed, only one very low test concentration was used.	**4**
Outcome unrelated to exposure		Were there differences in study groups that were unrelated to exposure that could influence the outcome? Only one	**1**

Short citation (Author, year, or ID)	**SPRIN91E**		
Full citation (or link)	**Springborn Laboratories, Inc. 1991e. Bioconcentration and Elimination of ^{14}C-residues by Fathead Minnows (*Pimephales promelas*) Exposed to Octamethylcyclotetrasiloxane. Supplemental Study. Report 91-6-3809; Springborn Laboratories, Inc. Wareham, MA. 70 pp.**		
Study type (e.g., OECD Guideline if applicable)	**EPA 797.1520**		
Study Director (if applicable)	**P.H. Fackler, Ph.D.**		
GLP Compliance (if applicable)	**Yes**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score***
		test concentration group was studied, but the outcome was related to exposure.	
Statistical methods	No statistics were discussed, nor were they needed since no mortality was observed.	Were statistical methods appropriate? No statistics were used for toxicity because no mortality was observed. Confidence intervals were used to define bioconcentration.	**1**
Estimate of variability	For mortality, no estimate of variability was made, but the report stated that no mortality was observed. It's possible that no fish died at all. For bioconcentration testing, confidence intervals were determined and unstable test concentrations were discussed.	Were unexpected outcomes explained and variability discussed? Yes, discussion was presented on the unstable test concentrations.	**2**
		Score (26–104):	**58***

Notes:

*The scores are based on the toxicity endpoint, not the bioconcentration endpoint.

Short citation (Author, year, or ID)	**WILDL08A**		
Full citation (or link)	**Wildlife International, Ltd. 2008. D4: a prolonged sediment toxicity test with *Chironomus riparius* using spiked sediment. Final report. Project number 570A-107.**		
Study type (e.g., OECD Guideline if applicable)	**OECD guideline 218**		
Study Director (if applicable)	**Krueger, H.O., S.T. Thomas, and T.Z. Kendall (Authors)**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	Origin: provided by Dow Purity: 99.75% active ingredient	Was the source and purity identified? Yes	**1**
Preparation	D4 was used to prepare the dosed sediment, matrix fortifications, and analytical calibration standards. Nominal test concentrations were prepared by mixing D4 in to air-dried peat. Next, formulated sediment was added and mixed. Well water (moderately hard) added.	Was test substance preparation described and appropriate for the test system? Yes	**1**
Test Design			
Test system (field, lab, static, flow-through, open/closed, etc.)	Lab, static, open system. Artificial sediment (targeted organic carbon content of 5.0%) spiked with D4.	Was the test system appropriate for the test substance and desired outcome(s)? Yes	**1**
Test conditions (test vessels, pH, temperature, media, etc.)	Vessel: 2 L test chamber contains sediment and overlying water. Vessel preparation: Prepared formulated sediment was added to test chambers for a 2 cm depth. 8 cm depth of well water was also added. Loose plastic covers placed over each chamber. Aeration: Yes, each chamber at a rate of >1 bubble/second using glass pipette. Water temperature: 19.7 – 20.5 °C. Test chambers were acclimated in a temperature controlled environmental chamber to condition the sediment prior to organism introduction. Dissolved oxygen ≥7.2 mg/L (80% saturation) Water pH: 8.2 – 8.6 Photoperiod: 16 hours light, 8 hours dark with 30 minute transition period	Were the test conditions appropriate? Yes	**1**

Short citation (Author, year, or ID)	**WILDL08A**		
Full citation (or link)	**Wildlife International, Ltd. 2008. D4: a prolonged sediment toxicity test with *Chironomus riparius* using spiked sediment. Final report. Project number 570A-107.**		
Study type (e.g., OECD Guideline if applicable)	**OECD guideline 218**		
Study Director (if applicable)	**Krueger, H.O., S.T. Thomas, and T.Z. Kendall (Authors)**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	Food: A 28 day supply of food was mixed into the test chambers 48 hours before adding the midges and after characterizing the sediment.		
Test organisms (species, age, health, handling)	Species: *Chironomus riparius* (midge) Age: 1-3 days old	Was the test species, age, etc. appropriate? Yes, but procedures for ensuring similarity in age were not well described.	**2**
Test organism acclimation	Duration: Egg masses were held for 24 hours prior to test initiation in the same temperature and water used for the test.	Were test organisms acclimated appropriately? Yes	**1**
Controls (negative, vehicle, positive)	Negative control	Were the appropriate controls used? Yes	**1**
Number of organisms and replicates per group	Eight replicates/group, divided into: Four replicates per exposure for biological samples (biological replicates). Four additional replicates were used for monitoring water quality and collecting analytical samples (analytical replicates). Two of the analytical replicates also contained midges. 20 organisms/replicate for a total of 80 midges per treatment group for the biological samples	Was the number of organisms and replicates per group appropriate? Yes	**1**
Number of exposure groups and spacing	Exposure: 28 days Exposure groups: 5 treatments plus negative control: 31, 63, 125, 250, 500, and 1000 mg/kg dry weight (nominal concentrations) The spacing of doses was a factor of 2.	Were the number of exposure groups and spacing between them appropriate? Yes, though no details provided on serial dilution decisions.	**2**
Randomized design	Test chambers were organized in a random design in a temperature controlled environmental chamber. Midges were impartially assigned to test chambers and added 1-2 at a time using pipettes.	Were organisms randomly allocated to groups? Yes	**1**
Exposure Characterization			

Short citation (Author, year, or ID)	**WILDL08A**		
Full citation (or link)	**Wildlife International, Ltd. 2008. D4: a prolonged sediment toxicity test with *Chironomus riparius* using spiked sediment. Final report. Project number 570A-107.**		
Study type (e.g., OECD Guideline if applicable)	**OECD guideline 218**		
Study Director (if applicable)	**Krueger, H.O., S.T. Thomas, and T.Z. Kendall (Authors)**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Testing at or below solubility	No details provided at testing at or below solubility.	Were exposure concentrations at or below the water solubility limit? Method was spiked sediment, so N/A. Was the solvent concentration appropriate? Unknown	**3**
Exposure consistency	A formulated sediment was used per the OECD guideline; sediment has been thoroughly characterized. No details provided on inconsistent testing conditions that may have affected results.	Were exposures consistent across groups? Yes	**1**
Exposure route and method (aqueous, via soil, etc.)	Sediment exposure. D4 was mixed with sediment and overlaid with water.	Was the exposure route and method appropriate? Yes	**1**
Exposure period (length, dosing frequency)	Exposure duration: 28 d Dosing frequency: static	Was the exposure frequency and duration appropriate? Yes	**1**
Treatment groups (concentrations/doses/rates)	The number of treatments was five: 31, 63, 125, 250, 500, and 1000 mg/kg dry weight (nominal concentrations); 6.5, 7.9, 19, 44, 131, and 355 mg/kg (mean measured) The spacing of doses was a factor of 2.	Was the number of groups and spacing of doses appropriate? Yes	**1**
Measurement of test substance concentration	D4 concentrations analyzed (following extraction) with gas chromatography with flame ionization detection. Calibration standards used. Use of internal standard. Recovery in QC samples ranged from 89.6 to 97.1% of nominal.	Were test substance concentrations measured if poorly water soluble? Yes	**1**
Methods and Observations			
Control organism performance	Mean development time for control organisms was assessed. Mean emergence ratio for control was 0.93. Mean development rate was 0.0572.	Were the biological responses of the negative control group adequate? Yes	**1**
Outcome assessment methodology	The outcome assessment included daily observations of mortality and clinical signs of toxicity or abnormal behavior. During emergence, sex and number of fully emerged adults were recorded. After identification, midges were removed from test chambers.	Was the outcome assessment methodology sensitive for the outcome(s) of interest? Yes	**1**
Consistency of outcome assessment	No inconsistencies in the execution of study methods or reporting of results were noted.	Was the outcome assessment done consistently across treatment groups? Yes	**1**

Short citation (Author, year, or ID)	**WILDL08A**		
Full citation (or link)	**Wildlife International, Ltd. 2008. D4: a prolonged sediment toxicity test with *Chironomus riparius* using spiked sediment. Final report. Project number 570A-107.**		
Study type (e.g., OECD Guideline if applicable)	**OECD guideline 218**		
Study Director (if applicable)	**Krueger, H.O., S.T. Thomas, and T.Z. Kendall (Authors)**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Sampling adequacy	Biological observations included mortality, emergence, and abnormal behavior and were made daily. Sediment samples were collected from the analytical replicate for each treatment on days 0, 7, and 28. Water quality measurements such as dissolved oxygen, pH, ammonia, hardness, alkalinity, and specific conductance were measured either daily or at the initiation and termination of the test	Was sampling adequate for the outcome(s) of interest?	
Confounding variables in design/procedures	No confounding variables noted.	Were there confounding differences among groups that could influence the outcome? No	**1**
Results			
Data	Yes, tables of raw data were reported. Results summary: 28 day LC50 for survival: 114 mg/kg with 95% confidence limits of 96 and 136 mg/kg NOEC: 44 mg/kg based on survival and emergence ratio LOEC: 131 mg/kg based on survival and emergence ratio Development rate was less sensitive	Were the data appropriately reported to document the outcome? Yes	**1**
Outcome unrelated to exposure	No biological outcomes unrelated to exposure (e.g., infections) were noted.	Were there differences in study groups that were unrelated to exposure that could influence the outcome? No	**1**
Statistical methods	LC50 calculated by probit analysis of mortality at 28 days. , NOEC and LOEC determined for survival, emergence, and development time using Duncan's test. No significant interactions between treatments and sex, so data for males and females were pooled.	Were statistical methods appropriate? Yes but tests for normality and homoscedasticity not mentioned.	**2**
Estimate of variability	No unexpected variability noted.	Were unexpected outcomes explained and variability discussed? N/A	1
		Score (26–104):	**30**

Short citation (Author, year, or ID)	**WILDL09A**		
Full citation (or link)	**Wildlife International, Ltd. 2009. Octamethylcyclotetrasiloxane (D4): a prolonged sediment toxicity test with *Lumbriculus variegatus* using spiked artificial sediment. Final report. Project number 570A-110B.**		
Study type (e.g., OECD Guideline if applicable)	**OPPTS 850.1735 guideline; ASTM standard E 1706-00; OECD guideline 225 though guideline was not adopted when the protocol was signed.**		
Study Director (if applicable)	**Krueger, H.O.**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	Origin: provided by Dow Purity: 99.75 %	Was the source and purity identified? Yes	**1**
Preparation	Formulated sediment (2.4% organic carbon) prepared. D4 added to peat that was then mixed with the remaining constituents. Sediment characterization documented based upon recipe. Test concentrations prepared on a dry weight basis. Well water (overlying water) filtered prior to use.	Was test substance preparation described and appropriate for the test system? Yes	**1**
Test Design			
Test system (field, lab, static, flow-through, open/closed, etc.)	Lab, Flow through compartments with sediment and overlying water. Water flow was limited to a four minute period twice a day, so exposure is considered semi-static	Was the test system appropriate for the test substance and desired outcome(s)? Yes	**1**
Test conditions (test vessels, pH, temperature, media, etc.)	Vessels: 300 mL test compartments Vessel preparation: Test compartments placed in stainless steel diluter tanks within a temperature controlled water bath. Test compartments contained formulated 100 mL sediment with test doses, and 150 mL of well water. One tank was assigned to each treatment or control. Dilution water was delivered twice a day. Compartments contained stainless steel mesh covered holes on opposite sides of the compartment to allow for flow of dilution water (784 mL/minute) for four minutes twice a day. Temperature: 23 ±1 °C, test compartments added to water bath for temperature control. Lighting: 16 hours light / 8 hours dark. Water circulation: Overlying water exchanged twice daily. Food: 28 day ration of food added to test compartment after sediment added and 48 hours prior to adding organisms.	Were the test conditions appropriate? Yes, however no mention of lid used in test compartment related to potential concern of D4 volatilizing that could have been enhanced due to flow of overlying water. As discussed in Nusz et al. (2018), the use of artificial sediment, with peat as the only source of organic matter, was a major weakness as microbiological biomass and microbiological contributions to organic matter in artificial sediments are up to 10-fold less than in natural sediments and a multitude of naturally occurring ligands are not present.	**4**

Short citation (Author, year, or ID)	**WILDL09A**		
Full citation (or link)	**Wildlife International, Ltd. 2009. Octamethylcyclotetrasiloxane (D4): a prolonged sediment toxicity test with *Lumbriculus variegatus* using spiked artificial sediment. Final report. Project number 570A-110B.**		
Study type (e.g., OECD Guideline if applicable)	**OPPTS 850.1735 guideline; ASTM standard E 1706-00; OECD guideline 225 though guideline was not adopted when the protocol was signed.**		
Study Director (if applicable)	**Krueger, H.O.**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test organisms (species, age, health, handling)	Species: *Lumbriculus variegatus* Age: Adults	Was the test species, age, etc. appropriate? Yes, however more information on age of organism could be added, or methods use to synchronize to same age.	**2**
Test organism acclimation	Duration: 14 day holding period prior to test initiation in water Temperature: 22.1 – 24.7 °C pH: 8.2 – 8.8 Dissolved oxygen: 7.1 – 8.4 mg/L. Food: Organisms fed during holding period.	Were test organisms acclimated appropriately? Yes	**1**
Controls (negative, vehicle, positive)	Negative control	Were the appropriate controls used? Yes, though little detail is provided on the negative control.	**1**
Number of organisms and replicates per group	10 organisms/vessel 8 biological replicates/group Additional details: 8 replicates per treatment for monitoring survival and growth (biological replicates) 5 replicates used as analytical replicates (2 analytical replicates contained organisms) The additional five analytical replicates per group were used for analytical sampling of sediment. Organisms added to one analytical replicate each for day 7 and day 28 analysis..	Was the number of organisms and replicates per group appropriate? Yes	**1**
Number of exposure groups and spacing	6 exposure groups: 3.8, 7.5, 15, 30, 60, and 120 mg/kg (nominal); 0.73, 1.5, 3.1, 5.8, 11, and 38 mg/kg (measured, in biotic replicates One negative control group	Were the number of exposure groups and spacing between them appropriate? Yes	**1**
Randomized design	Test organisms impartially assigned to test compartment one or two at a time until each chamber contained 10 organisms. Test compartments randomly positioned inside a diluter unit according to the treatment group. Compartments positioned 48 hours prior to initiation for sediment conditioning.	Were organisms randomly allocated to groups? Yes	**1**
Exposure Characterization			

Short citation (Author, year, or ID)	**WILDL09A**		
Full citation (or link)	**Wildlife International, Ltd. 2009. Octamethylcyclotetrasiloxane (D4): a prolonged sediment toxicity test with *Lumbriculus variegatus* using spiked artificial sediment. Final report. Project number 570A-110B.**		
Study type (e.g., OECD Guideline if applicable)	**OPPTS 850.1735 guideline; ASTM standard E 1706-00; OECD guideline 225 though guideline was not adopted when the protocol was signed.**		
Study Director (if applicable)	**Krueger, H.O.**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Testing at or below solubility	Water solubility recorded as 56.2 µg/L using preliminary trials.	Were exposure concentrations at or below the water solubility limit? Exposure via spiked sediment, so NA Was the solvent concentration appropriate? No solvent was used, N/A	**2**
Exposure consistency	Sediment concentrations measured at 0, 7 and 28 days. Standard deviation of means, calculated using day 0 results and biotic replicates, is 19 to 20%.	Were exposures consistent across groups? Yes, however discussion of results from abiotic replicates not provided. .	**2**
Exposure route and method (aqueous, via soil, etc.)	Sediment exposure. D4 was mixed into sediment to provide different concentrations	Was the exposure route and method appropriate? Yes	**1**
Exposure period (length, dosing frequency)	Exposure duration: 28 days Dosing frequency: one dose in sediment	Was the exposure frequency and duration appropriate? Yes	**1**
Treatment groups (concentrations/doses/rates)	6 treatments and negative control 8 replicates per treatment for biological samples, 5 additional replicates for analytical samples (2 of the analytical replicates had organisms)	Was the number of groups and spacing of doses appropriate? Yes	**1**
Measurement of test substance concentration	Samples were extracted and analyzed with gas chromatography with mass selective detector. Calibration standards, calibration curve, and internal standard used. Fortified samples also analyzed (recovery 55.4 to 110%).	Were test substance concentrations measured if poorly water soluble? Yes	**1**
Methods and Observations			
Control organism performance	Observations for mortality and abnormal behavior made daily. Survivorship and growth were measured after termination at 28 days.	Were the biological responses of the negative control group adequate? Yes	**1**
Outcome assessment methodology	The outcome assessment included daily observations of mortality and clinical signs of toxicity or abnormal behavior. Not possible to differentiate between adults and young, so survival and reproduction were considered one endpoint. Dry weight was measured at days 0 and 28.	Was the outcome assessment methodology sensitive for the outcome(s) of interest? Yes	**1**
Consistency of outcome assessment	No inconsistencies in the execution of study methods or reporting of results were noted.	Was the outcome assessment done consistently across treatment groups? Yes	**1**

Short citation (Author, year, or ID)	**WILDL09A**		
Full citation (or link)	**Wildlife International, Ltd. 2009. Octamethylcyclotetrasiloxane (D4): a prolonged sediment toxicity test with *Lumbriculus variegatus* using spiked artificial sediment. Final report. Project number 570A-110B.**		
Study type (e.g., OECD Guideline if applicable)	**OPPTS 850.1735 guideline; ASTM standard E 1706-00; OECD guideline 225 though guideline was not adopted when the protocol was signed.**		
Study Director (if applicable)	**Krueger, H.O.**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Sampling adequacy	Live and dead organisms counted at day 28. Dry weight measured at day 28. 20 additional organisms used for initial dry weight measurements and were not used in the test. Temperature and dissolved oxygen measured daily in one alternating replicate. pH measured at initiation, weekly, and at termination in one alternating replicate. Hardness, alkalinity, specific conductance, and ammonia measured in control replicates and highest treatment group at initiation and termination. Analytical samples for sediment and water collected on days 0, 7, and 28.	Was sampling adequate for the outcome(s) of interest? Yes	**1**
Confounding variables in design/procedures	No confounding variables noted.	Were there confounding differences among groups that could influence the outcome? No	**1**
Results			
Data	Yes, tables of raw data were provided. Results summary: 28 Day EC50: 9.32 mg/Kg with 95% confidence limits of 4.38 and 25.4 mg/Kg, based on survival and reproduction. NOEC: <0.73 mg/Kg and LOEC: 0.73 mg/Kg, based on survival. No effects on dry weight.	Were the data appropriately reported to document the outcome? Yes	**1**
Outcome unrelated to exposure	No biological outcomes unrelated to exposure (e.g., infections) were noted.	Were there differences in study groups that were unrelated to exposure that could influence the outcome? No	**1**
Statistical methods	EC50, NOEC, LOEC based on survival/reproduction and growth as endpoints. Dry weight at day 0 and 28. TOXSTAT program used Chi-Square Test for normality and Levene's or Bartlett's Tests for homogenous variance. Dunnett's test used for significance between treatment levels. Method limit of quantitation used.	Were statistical methods appropriate? Yes	**1**

Short citation (Author, year, or ID)	**WILDL09A**		
Full citation (or link)	**Wildlife International, Ltd. 2009. Octamethylcyclotetrasiloxane (D4): a prolonged sediment toxicity test with *Lumbriculus variegatus* using spiked artificial sediment. Final report. Project number 570A-110B.**		
Study type (e.g., OECD Guideline if applicable)	**OPPTS 850.1735 guideline; ASTM standard E 1706-00; OECD guideline 225 though guideline was not adopted when the protocol was signed.**		
Study Director (if applicable)	**Krueger, H.O.**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Estimate of variability	An initial trial was repeated at lower concentrations to achieve the NOEC. A second trial was repeated due to low reproduction. Occurrence of reproduction and differentiation between adults and young is not possible. Therefore, survival and reproduction were considered one endpoint with total number of organisms counted at test termination.	Were unexpected outcomes explained and variability discussed? Yes, however more detail was needed to the rationale for why some of the trials were repeated.	2
		Score (26–104):	**33**
Note: The quality of this study is compromised by the use of artificial sediment.			

Short citation (Author, year, or ID)	**SPRIN09A**		
Full citation (or link)	**Springborn Smithers Laboratories. 2009. D4 – sediment-water *Lumbriculus* toxicity test using spiked sediment, following OECD guideline 225. Study number: 13937.6103.**		
Study type (e.g., OECD Guideline if applicable)	**OECD guideline 225**		
Study Director (if applicable)	**Picard, C.R. (Author and Director)**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	D4	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	Origin: provided by Dow Purity: 99.77%	Was the source and purity identified? Yes	**1**
Preparation	Stock solution preparation of D4, diluted with acetone. The sediment was spiked as follows: 2.5 kg wet sediment with 7.5 L overlying water in individual glass jars. Contents were shaken prior to and after dosing. Stock solution added to test jars. A 16 hour settling period occurred following by decanting the water and transferring the sediment for mixing and reallocation into test vessels. Food was added to the sediment. Sediment and well water characterized prior to experiment.	Was test substance preparation described and appropriate for the test system? Yes	**1**
Test Design			
Test system (field, lab, static, flow-through, open/closed, etc.)	Lab, static with aeration, semi-closed system, sediment test system overlaid with characterized well water. Natural sediment used (2.2% organic carbon). Test vessels covered with clear plastic plate to minimize evaporation.	Was the test system appropriate for the test substance and desired outcome(s)? Yes	**1**
Test conditions (test vessels, pH, temperature, media, etc.)	Vessel: 600 mL glass beakers Vessel set up: Prepared sediment and overlying water were added to test vessels (600 mL glass beakers) two days prior to test initiation. 75 mL of test sediment was added and 300 mL of overlying water. Closed system: Beakers covered to reduce evaporation. Overlying water: Fortified well water. Total hardness: 170 mg/L as $CaCO_3$, Alkalinity:100 mg/L as $CaCO_3$, pH: 8.0. Specific conductance: 600 micromhos/cm. Duration: 28 day Temperature: 19-23 °C, Dissolved oxygen (DO): 7.4 to 9.2 mg/L,	Were the test conditions appropriate? Yes	**1**

Short citation (Author, year, or ID)	**SPRIN09A**		
Full citation (or link)	**Springborn Smithers Laboratories. 2009. D4 – sediment-water *Lumbriculus* toxicity test using spiked sediment, following OECD guideline 225. Study number: 13937.6103.**		
Study type (e.g., OECD Guideline if applicable)	**OECD guideline 225**		
Study Director (if applicable)	**Picard, C.R. (Author and Director)**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	pH: 7.2 to 8.1 Lighting: 16 hours light : 8 hours dark, 530 to 540 lux Aeration: Yes, occurred 2-3 cm above sediment at 1-3 bubbles per second. Additional test conditions the same as acclimation conditions.		
Test organisms (species, age, health, handling)	*Lumbriculus variegatus* Age: Two weeks prior to test initiation, worms were removed from the culture and artificially fragmented to synchronize the population using a scalpel.	Was the test species, age, etc. appropriate? Yes	**1**
Test organism acclimation	Duration: Synchronized worms were acclimated to test conditions (water and sediment) 13 days prior and allowed to regenerate new heads. Acclimation vessel: 57 L aquaria with 40 L culture water with flow through conditions. Acclimated to test water and test sediment. Food: Synchronized worms were fed 6.4 mL of flaked fish food once during acclimation. No mortality was observed in the test population 48 hours prior to test initiation.	Were test organisms acclimated appropriately? Yes	**1**
Controls (negative, vehicle, positive)	Solvent control sample using acetone. Negative control used untreated sediment and overlying water.	Were the appropriate controls used? Yes	**1**
Number of organisms and replicates per group	Four replicates/group except six replicates/group for control and solvent control (biological replicates) Four replicates/group (analytical replicates) 10 organisms;/vessel Additional details: 10 worms per replicate vessel, for a total of 40 worms per treatment and 60 worms per control. The additional replicates for chemical analysis each contained 10 worms.	Was the number of organisms and replicates per group appropriate? Yes	**1**
Number of exposure groups and spacing	6 groups: 3.1, 6.3, 13, 25, 50, and 100 mg/kg (nominal sediment concentrations); 1.2, 3.2, 8.8, 13, 19, and 32 mg/kg (mean measured sediment concentrations).	Were the number of exposure groups and spacing between them appropriate? Yes	**1**

Short citation (Author, year, or ID)	**SPRIN09A**		
Full citation (or link)	**Springborn Smithers Laboratories. 2009. D4 – sediment-water *Lumbriculus* toxicity test using spiked sediment, following OECD guideline 225. Study number: 13937.6103.**		
Study type (e.g., OECD Guideline if applicable)	**OECD guideline 225**		
Study Director (if applicable)	**Picard, C.R. (Author and Director)**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	Exposure concentrations determined during preliminary testing.		
Randomized design	Organisms added impartially by adding no more than two organisms to each vessel until all vessels were filled with ten organisms.	Were organisms randomly allocated to groups? Yes	**1**
Exposure Characterization			
Testing at or below solubility	No details provided on solubility testing	Were exposure concentrations at or below the water solubility limit? Method was spiked sediment, so NA Was the solvent concentration appropriate? Unknown	**3**
Exposure consistency	D4 dosing occurred once during the test (static conditions). Concentrations in sediment measured at initiation, day 7 and termination to confirm dose consistency.	Were exposures consistent across groups? Yes	**1**
Exposure route and method (aqueous, via soil, etc.)	Sediment/aqueous exposure. D4 was mixed with a solvent and stock solutions spiked into sediment.	Was the exposure route and method appropriate? Yes	**1**
Exposure period (length, dosing frequency)	Exposure duration: 28 days Dosing frequency: static	Was the exposure frequency and duration appropriate? Yes	**1**
Treatment groups (concentrations/doses/rates)	6 treatments: 3.1, 6.3, 13, 25, 50, and 100 mg/kg (nominal sediment concentrations). The spacing of nominal doses was approximately a factor of 2. Static dose for each of the six exposure concentrations.	Was the number of groups and spacing of doses appropriate? Yes.	**1**
Measurement of test substance concentration	Gas chromatography with mass selective detection with validated method (recovery 101 ± 28.1% in natural sediment). Defined limits set for quality control performance. An internal standard was used to quantify D4 concentrations in the test samples and quality control samples.	Were test substance concentrations measured if poorly water soluble? Yes. One of the 9 QC samples were out of control and one was prepared incorrectly.	**2**
Methods and Observations			
Control organism performance	Daily biological observations included mortality and abnormal behavior (leaving sediment). Final measurements on day 28 included mortality and surviving biomass. Surviving worms	Were the biological responses of the negative control group adequate? Yes, met minimum performance criteria (increase in living worms in control by a factor > 1.8)	**1**

Short citation (Author, year, or ID)	**SPRIN09A**		
Full citation (or link)	**Springborn Smithers Laboratories. 2009. D4 – sediment-water *Lumbriculus* toxicity test using spiked sediment, following OECD guideline 225. Study number: 13937.6103.**		
Study type (e.g., OECD Guideline if applicable)	**OECD guideline 225**		
Study Director (if applicable)	**Picard, C.R. (Author and Director)**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	were placed into three categories based on size and regeneration post-experiment.		
Outcome assessment methodology	Biological observations, water quality measurements, and D4 concentrations in sediment were recorded during test.	Was the outcome assessment methodology sensitive for the outcome(s) of interest? Yes	**1**
Consistency of outcome assessment	No inconsistencies in the execution of study methods or reporting of results were noted.	Was the outcome assessment done consistently across treatment groups? Yes	**1**
Sampling adequacy	Exposure concentrations measured on days 0, 7, and 28. Water quality measurements (DO, temperature and pH) occurred in all replicates on days 0 and 28 and in one replicate each day. Additional water quality measurements were determined only for the highest treatment level and included total hardness, alkalinity, specific conductivity, and ammonia. Ammonia was measured three times a week in the solvent control and highest treatment level. Initial water levels in test vessels was noted to monitor evaporation.	Was sampling adequate for the outcome(s) of interest? Yes	**1**
Confounding variables in design/procedures	No confounding variables noted.	Were there confounding differences among groups that could influence the outcome? No	**1**
Results			
Data	Yes, tables of raw data were reported. Results summary: Survival was affected in the two highest concentrations. Based on measured concentrations of D4 in the sediment, the No-Observed-Effect Concentration (NOEC) for this exposure was determined to be 13 mg/kg. The Lowest-Observed-Effect Concentration (LOEC) for this exposure was determined to be 19 mg/kg. Biomass was not affected. Since no concentration tested resulted in ≥ 50% reduction in survival or biomass, the EC50 value was empirically estimated to be > 32 mg/kg, the highest mean measured concentration tested.	Were the data appropriately reported to document the outcome? Yes	**1**
Outcome unrelated to exposure	No biological outcomes unrelated to exposure (e.g., infections) were noted.	Were there differences in study groups that were unrelated to exposure that could influence the outcome? No	**1**

Short citation (Author, year, or ID)	**SPRIN09A**		
Full citation (or link)	**Springborn Smithers Laboratories. 2009. D4 – sediment-water *Lumbriculus* toxicity test using spiked sediment, following OECD guideline 225. Study number: 13937.6103.**		
Study type (e.g., OECD Guideline if applicable)	**OECD guideline 225**		
Study Director (if applicable)	**Picard, C.R. (Author and Director)**		
GLP Compliance (if applicable)	**Y**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Statistical methods	All statistical analyses were conducted at the 95% level of certainty, except for Chi-Square and Bartlett's Tests, which were conducted at 99% level of certainty. T test conducted for reproduction and biomass data to compare control to solvent control data; no significant difference for either endpoint (reproduction or biomass) so comparisons were made to the pooled control. Bonferroni's T test used to establish effects (LOEC and NOEC) for reproduction and biomass. EC50 determined empirically.	Were statistical methods appropriate? Yes	**1**
Estimate of variability	On day 17 replicate D of the 6.3 mg/kg nominal treatment level had a DO measurement of 3.8 mg/L due to a malfunction in the aeration system. Aeration was restored and dissolved oxygen levels returned to the range stated in the protocol. Other protocol deviations recorded, but expected these did not affect the results of the study.	Were unexpected outcomes explained and variability discussed? Yes	1
		Score (26–104):	**29**

Short citation (Author, year, or ID)	**WILDL08B**		
Full citation (or link)	**Octamethylcyclotetrasiloxane (D4): A 96-hour study of the elimination and metabolism of orally gavaged 14C-D4 in rainbow trout (*Oncorhynchus mykiss*). HES study number: 10710-101. Wildlife International Ltd. Project No. 406A-112**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**Springer, T.A.**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	^{14}C-D4	Was the test substance identified definitively? Yes,	**1**
Composition (purity, origin); single substance (not mixture)	Origin: Individual vials provided for each trial, provided by Dow Purity: specific activity 6.883 mCi/g.	Was the source and purity identified? Yes, however no purity detail described. Should be noted that 14C-D4 was provided. Specific activity provided although was reported in the water solubility column	**2**
Preparation	14C-D4 dissolved in corn oil, to get target dose in fish of 15 mg D4/kg fish; Fish anaesthetized and cannula inserted into aorta for each fish for blood sampling and catheter inserted for urine sampling.	Was test substance preparation described and appropriate for the test system? Yes	**1**
Test Design			
Test system (field, lab, static, flow-through, open/closed, etc.)	Study was designed to investigate metabolism, tissue distribution, and elimination of orally-administered D4. Fish kept under laboratory, flow through conditions	Was the test system appropriate for the test substance and desired outcome(s)? Yes	**1**
Test conditions (test vessels, pH, temperature, media, etc.)	Vessel: Plexiglas test chamber with aeration and partitioning to partially separate water surrounding head and gills from the body. Fish dosed with oral gavage then held in individual test chambers for 96 hours with Contact flow of 13.1-14.6 °C water. Lighting: 16 hours light : 8 hours dark. Aeration: Yes Final endpoint: 96 hours Trial One: radioactivity and parent material in fish determined in various biological samples collected. Trial Two: initiated 10 days after Trial One. Urine profiled for metabolites.	Were the test conditions appropriate? Yes	**1**

Short citation (Author, year, or ID)	**WILDL08B**		
Full citation (or link)	**Octamethylcyclotetrasiloxane (D4): A 96-hour study of the elimination and metabolism of orally gavaged 14C-D4 in rainbow trout (*Oncorhynchus mykiss*). HES study number: 10710-101. Wildlife International Ltd. Project No. 406A-112**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**Springer, T.A.**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test organisms (species, age, health, handling)	Rainbow trout (*Oncorhynchus mykiss*); 8 organisms total; 4 organisms/trial; 1 organisms/vessel (4 vessels/trial) Mature males weighing between 0.967 – 1.377 kg and appeared healthy.	Was the test species, age, etc. appropriate? Yes	**1**
Test organism acclimation	Duration: Test fish held for two weeks prior to trials Conditions: acclimated in same water to be used in trials and at the same temperature. Food: Fish fed once daily. Food withheld 24 hours prior to surgery.	Were test organisms acclimated appropriately? Yes	**1**
Controls (negative, vehicle, positive)	Negative control – one untreated fish	Were the appropriate controls used? Yes	**1**
Number of organisms and replicates per group	Two trials Four fish per trial Single dose used in both trials	Was the number of organisms and replicates per group appropriate? Yes	**1**
Number of exposure groups and spacing	15 mg/kg nominal dose Trial One: four mature rainbow trout Trail Two: four mature rainbow trout No dose spacing.	Were the number of exposure groups and spacing between them appropriate? Yes	**1**
Randomized design	No details on randomized design or impartiality in assigning fish to aquaria.	Were organisms randomly allocated to groups? No	**3**
Exposure Characterization			
Testing at or below solubility	Dose elected based upon previous work by Dow. No details on solubility testing.	Were exposure concentrations at or below the water solubility limit? Unknown – mentioned based on work previously conducted by Dow but not supporting information provided. Was the solvent concentration appropriate? Unknown.	**3**
Exposure consistency	No details indicating inconsistency in exposure. All fish were exposed by oral gavage and were in individual test chambers for 96 hours. One extra untreated fish used to determine background levels	Were exposures consistent across groups? Yes	**1**

Short citation (Author, year, or ID)	**WILDL08B**		
Full citation (or link)	**Octamethylcyclotetrasiloxane (D4): A 96-hour study of the elimination and metabolism of orally gavaged 14C-D4 in rainbow trout (*Oncorhynchus mykiss*). HES study number: 10710-101. Wildlife International Ltd. Project No. 406A-112**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**Springer, T.A.**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Exposure route and method (aqueous, via soil, etc.)	Oral gavage	Was the exposure route and method appropriate? Yes	**1**
Exposure period (length, dosing frequency)	Exposure duration: 96 hours Exposure dose: single dose of 15 mg/kg	Was the exposure frequency and duration appropriate? Yes	**1**
Treatment groups (concentrations/doses/rates)	Two trials Four fish in each trial	Was the number of groups and spacing of doses appropriate? Four replicates were appropriate for each trial, however only one exposure dose was used whereas two would be preferable.	**2**
Measurement of test substance concentration	Liquid scintillation counting (for dosing solution and samples of oil and water in test tanks) Blood, urine, bile, liver, digestive tract, fat, carcasses, fecal and milt samples were shipped to Dow Corning for analysis. This used tetrahydrofuran extraction followed by radioconcentration analysis and total activity of 14C-D4 in samples. Parent D4 was quantified using GC/MS and metabolites examined by HPLC/RAD.	Were test substance concentrations measured if poorly water soluble? Yes	**1**
Methods and Observations			
Control organism performance	No details provided on observations of test organisms during the trials.	Were the biological responses of the negative control group adequate? Not provided	**2**
Outcome assessment methodology	Outcome assessment included testing metabolism, tissue distribution, and elimination of D4.	Was the outcome assessment methodology sensitive for the outcome(s) of interest? Yes	**1**
Consistency of outcome assessment	No inconsistencies in the execution of study methods or reporting of results were noted that may have affected the study results.	Was the outcome assessment done consistently across treatment groups? Yes	**1**
Sampling adequacy	Fish euthanized at 96 hours. Blood and urine samples collected at 0, 2, 4, 8, 12, 24, 48, 72, and 96 hour intervals. Other tissues sampled at 96 hours Concentrations of parent D4 and total radioactivity were determined for bile, blood, digestive tract, testes (with milt), fat, and liver using liquid scintillation counting. Total radioactivity also determined for carcass, urine, and feces.	Was sampling adequate for the outcome(s) of interest? Yes	**1**

Short citation (Author, year, or ID)	**WILDL08B**		
Full citation (or link)	**Octamethylcyclotetrasiloxane (D4): A 96-hour study of the elimination and metabolism of orally gavaged 14C-D4 in rainbow trout (*Oncorhynchus mykiss*). HES study number: 10710-101. Wildlife International Ltd. Project No. 406A-112**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**Springer, T.A.**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	Urine samples collected for metabolite profile using HPLC/RAD. Well water characterization. Dissolved oxygen measured daily during test. After dosing any oil observed on the surface of the water was collected and analyzed with liquid scintillation counting. Total radioactivity measured with liquid scintillation counting. Biological samples were shipped to the study sponsor for analysis. Fish weighed prior to trials. Analytical verification of dosing solution.		
Confounding variables in design/procedures	Confounding variables are related to the urinary profile lacking an important intermediate found in usual metabolic degradation that is seen in rats and humans, and may be attributed to confounding factors such as age, sex, life stage, or physical and chemical properties of the test compound. Also, proportion of radioactivity in the fish carcass representing metabolites is unknown, therefore if metabolites are accounting for the high level of radioactivity found in the fish carcass then it would be expected that metabolism of the compound is more robust than is apparent from the current data set.	Were there confounding differences among groups that could influence the outcome? Yes, however explanations were provided to explain some of the variables.	**1**
Results			
Data	Yes, tables of raw data reported. Results summary: 79% of administered dose recovered. 82% of dose was absorbed. 69% of radioactivity found in the fish carcass. Out of total radioactivity measured the 95% found in the bile and 40% found in the liver was attributed to metabolites. 18% of	Were the data appropriately reported to document the outcome? Yes	**1**

Short citation (Author, year, or ID)	**WILDL08B**		
Full citation (or link)	**Octamethylcyclotetrasiloxane (D4): A 96-hour study of the elimination and metabolism of orally gavaged 14C-D4 in rainbow trout (*Oncorhynchus mykiss*). HES study number: 10710-101. Wildlife International Ltd. Project No. 406A-112**		
Study type (e.g., OECD Guideline if applicable)	**N**		
Study Director (if applicable)	**Springer, T.A.**		
GLP Compliance (if applicable)	**N**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	recovered dose was eliminated in the feces and was the parent compound. Urinary excretion was a minor elimination pathway.		
Outcome unrelated to exposure	No biological outcomes unrelated to exposure (e.g., infections) were noted. Some oil was observed on the surface of the chambers but was never more than 0.7% of the dose administered, except in one chamber in Trial 2 where it did not affect study results.	Were there differences in study groups that were unrelated to exposure that could influence the outcome? Sufficient explanation provided.	**2**
Statistical methods	Mean and standard deviations of concentrations measured in samples. Elimination half-life determined by Dow using PK solutions software.	Were statistical methods appropriate? Yes	**1**
Estimate of variability	Fish 9 had blood collected from cardiac puncture rather than the aortic cannula.	Were unexpected outcomes explained and variability discussed? Yes	1
		Score (26–104):	**34**
Note: this study contains data that appear in DOMOR17A. WILD08B is the companion internal report for the peer-reviewed DOMOR17A publication.			

Short citation (Author, year, or ID)	**DOMOR17B**		
Full citation (or link)	**Domoradzki, J.Y., J.M. Sushynski, L.M. Thackery, T.A. Springer, T.L. Ross, K.B. Woodburn, J.A. Durham, and D.A. McNett. 2017. Metabolism of 14C-octamethylcyclotetrasiloxane ([14C] D4) or 14C-decamethylcyclopentasiloxane ([14C] D5) orally gavaged in rainbow trout (*Oncorhynchus mykiss*). Toxicology Letters 279: 115–124.**		
Study type (e.g., OECD Guideline if applicable)	**Peer-reviewed literature. Laboratory study on in vivo fish metabolism.**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Test Substance			
Identity	14C-D4 and 14C-D5. Only D4 results discussed here	Was the test substance identified definitively? Yes	**1**
Composition (purity, origin); single substance (not mixture)	Source: provided by Dow Purity: Specific activity of 6.883 mCi/g Single substance: yes, tagged with isotope	Was the source and purity identified? Yes	**1**
Preparation	Individual dosing solutions prepared in corn oil of 30 mg/L of D4 for target dose of 15 mg D4 per kg fish tissue. The dose was prepared so a single dose could be delivered in a single 0.5 mL/kg body weight bolus oral gavage dose. Fish surgically prepared prior for catheter and a cannula. Confirmation of placement and overnight recovery occurred.	Was test substance preparation described and appropriate for the test system? Yes	**1**
Test Design			
Test system (field, lab, static, flow-through, open/closed, etc.)	Oral gavage in laboratory. Two D4 trials were conducted	Was the test system appropriate for the test substance and desired outcome(s)? Yes	**1**
Test conditions (test vessels, pH, temperature, media, etc.)	Lighting: 16 hours light : 8 hours dark. Temperature: Constant temperature (12±2ºC) and oxygen level (8.1-10.8 ppm) maintained in tests. Test vessel: Test vessels/aquaria not described. Test initiation: 0-hour blood sample collected then fish given oral bolus.	Were the test conditions appropriate? Yes	**1**
Test organisms (species, age, health, handling)	Species: Mature rainbow trout (*Oncorhynchus mykiss*) Age: unknown Size: Mature males between 1.0-1.4 kg were used for D4. Observations: Fish appeared healthy at initiation	Was the test species, age, etc. appropriate? Yes, though more details on age or length of fish could have been provided. Total number of fish used, or per replicate, was not described.	**2**
Test organism acclimation	Duration: Two week acclimation,	Were test organisms acclimated appropriately? Yes	**1**

Short citation (Author, year, or ID)	**DOMOR17B**		
Full citation (or link)	**Domoradzki, J.Y., J.M. Sushynski, L.M. Thackery, T.A. Springer, T.L. Ross, K.B. Woodburn, J.A. Durham, and D.A. McNett. 2017. Metabolism of 14C-octamethylcyclotetrasiloxane ([14C] D4) or 14C-decamethylcyclopentasiloxane ([14C] D5) orally gavaged in rainbow trout (*Oncorhynchus mykiss*). Toxicology Letters 279: 115–124.**		
Study type (e.g., OECD Guideline if applicable)	**Peer-reviewed literature. Laboratory study on in vivo fish metabolism.**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
	Food: Fed daily, food withheld 24 hours prior to initiation of test		
Controls (negative, vehicle, positive)	No details on controls.	Were the appropriate controls used? No details on controls; however they are not considered necessary for this type of study	**-**
Number of organisms and replicates per group	No details provided.	Was the number of organisms and replicates per group appropriate? Tables and Figures indicated n=4	**2**
Number of exposure groups and spacing	One exposure group	Were the number of exposure groups and spacing between them appropriate? Appropriate for study objectives. .	**2**
Randomized design	No randomization.	Were organisms randomly allocated to groups? No, lack of randomization was described: supply of 1 kg trout was limited and gender of the fish available varied over time. Therefore, gender could not be randomized within tests and the two compounds were tested using different genders.	**3**
Exposure Characterization			
Testing at or below solubility	No details provided.	Were exposure concentrations at or below the water solubility limit? Not relevant since not exposed via water. Was the solvent concentration appropriate? Not relevant	**-**
Exposure consistency	No details provided.	Were exposures consistent across groups? No details provided.	**3**
Exposure route and method (aqueous, via soil, etc.)	Oral through use of bolus and gavage.	Was the exposure route and method appropriate? Yes, relates to uptake via food which is more relevant for chemicals of high lipophilicity and low water solubility	**1**
Exposure period (length, dosing frequency)	Exposure duration: Final time point was 96 hours Dosing frequency: One single dose	Was the exposure frequency and duration appropriate? Yes	**1**

Short citation (Author, year, or ID)	**DOMOR17B**		
Full citation (or link)	**Domoradzki, J.Y., J.M. Sushynski, L.M. Thackery, T.A. Springer, T.L. Ross, K.B. Woodburn, J.A. Durham, and D.A. McNett. 2017. Metabolism of 14C-octamethylcyclotetrasiloxane ([14C] D4) or 14C-decamethylcyclopentasiloxane ([14C] D5) orally gavaged in rainbow trout (*Oncorhynchus mykiss*). Toxicology Letters 279: 115–124.**		
Study type (e.g., OECD Guideline if applicable)	**Peer-reviewed literature. Laboratory study on in vivo fish metabolism.**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Treatment groups (concentrations/doses/rates)	Individual dosing solutions prepared in corn oil of 30 mg/L of D4 for target dose of 15 mg D4 per kg fish tissue. No details on control treatments.	Was the number of groups and spacing of doses appropriate? The dose was similar to that used in a bioaccumulation study by Woodburn et al. (2013)	**1**
Measurement of test substance concentration	A stable isotope isomer served as the internal standard. Biological samples underwent extraction and were analyzed with gas chromatography. Radioactivity quantified with liquid scintillation analysis .Remaining biological samples (urine, bile, liver, digestive tract) were analyzed with HPLC-RAD.	Were test substance concentrations measured if poorly water soluble? Yes	**1**
Methods and Observations			
Control organism performance	Fish monitored for physical conditions and signs of regurgitation.	Were the biological responses of the negative control group adequate? No negative control described, however details provided on biological responses observed.	**1**
Outcome assessment methodology	The outcome assessment included determining D4 concentrations in various fish tissue, urine, blood, fecal material samples.	Was the outcome assessment methodology sensitive for the outcome(s) of interest? Yes	**1**
Consistency of outcome assessment	No inconsistencies in the execution of study methods or reporting of results were noted. However, urine samples were not collected in the first D4 trial.	Was the outcome assessment done consistently across treatment groups?	**2**
Sampling adequacy	Water chemistry tests: hardness, alkalinity, specific conductance was measured. Biological measurements: Fish weighted prior to dose, and after dose. Blood samples collected from each fish at 0, 2, 4, 8, 12, 24, 48, 72, and 96 hours post-dose. Urine samples collected at following intervals: 0-2, 2-4, 4-8, 8-12, 12-24, 24-48, 48-72, and 72-96 hours. 0-hour urine collection occurred prior to test initiation. Fecal samples collected at 0-24, 24-48, 48-72, and 72-96 hours. Biological samples collected after euthanasia.	Was sampling adequate for the outcome(s) of interest? Yes	**1**
Confounding variables in design/procedures	No confounding variables noted.	Were there confounding differences among groups that could influence the outcome? No	**1**

Short citation (Author, year, or ID)	**DOMOR17B**		
Full citation (or link)	**Domoradzki, J.Y., J.M. Sushynski, L.M. Thackery, T.A. Springer, T.L. Ross, K.B. Woodburn, J.A. Durham, and D.A. McNett. 2017. Metabolism of 14C-octamethylcyclotetrasiloxane ([14C] D4) or 14C-decamethylcyclopentasiloxane ([14C] D5) orally gavaged in rainbow trout (*Oncorhynchus mykiss*). Toxicology Letters 279: 115–124.**		
Study type (e.g., OECD Guideline if applicable)	**Peer-reviewed literature. Laboratory study on in vivo fish metabolism.**		
Study Director (if applicable)	**N/A**		
GLP Compliance (if applicable)	**N/A**		
Information Element	**Information Capture**	**Evaluation Criteria**	**Score**
Results			
Data	No, raw data tables not presented. Additional data tables presented in supplemental information. Results summary: Of the administered dose, 79% (D4) was recovered by the end of the study (96-h); a significant portion was eliminated in feces. Approximately 40% of the total radioactivity in the liver was due to metabolites. Using mean residue data, the estimated metabolism rate constant was 0.10 day^{-1} Assuming first- order kinetics, the resulting fish metabolism half-life for D4 is approximately 6.7 days and the overall D4 dissipation half-life (metabolism + loss due to elimination/storage) in trout was approximately 1.2 days. Clearance may occur via enterohepatic circulation of metabolic products in bile with excretion via the digestive tract and urinary clearance of polar metabolites.	Were the data appropriately reported to document the outcome? Data tables and figures in main text, though are not the raw data tables. Additional data in supplemental material.	**1**
Outcome unrelated to exposure	No biological outcomes unrelated to exposure (e.g., infections) were noted.	Were there differences in study groups that were unrelated to exposure that could influence the outcome? No	**1**
Statistical methods	Means and standard deviation. Blood area under the curve for parent and radioactivity analyses were calculated with SSS/STAT software. Metabolic rate constant determined based on assumption of first-order kinetics .	Were statistical methods appropriate? Yes, however no information on goodness of fit.	**2**
Estimate of variability	No unexpected variability described.	Were unexpected outcomes explained and variability discussed? No unexpected variability described.	1
		Score (26–104); without two criteria, possible score was 24-96:	**33**
Note: DOMOR17B is the peer-reviewed version of data developed in WILD08B.			

Short citation (Author, year, or ID)	**BRIDG16A; BRIDG16B (SI)**
Full citation (or link)	**Bridges, J., and K.R. Solomon. 2016. Quantitative weight-of-evidence analysis of the persistence, bioaccumulation, toxicity, and potential for long-range transport of the cyclic volatile methyl siloxanes. *Journal of Toxicology and Environmental Health, Part B* 19(8): 345-379.**
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature providing a weight-of-evidence analysis of fate, transport, toxicity and bioaccumulation**
Study Director (if applicable)	**N/A**
GLP Compliance (if applicable)	**N/A**

Discussion: No new data presented but article evaluates available studies on persistence, bioaccumulation and toxicity of cVMS in a standardized process. Used quantitative scoring or expert judgement to assign quality and relevance to each study. Extensive review of studies on persistence, toxicity, bioaccumulation in the SI. (Note: Downgraded the *L. variegatus* study with artificial sediment (WILDL09A) due to use of peat.) Reviews data on occurrence and properties related to persistence, concluding that cVMSs should not be classified as persistent. Studies in food webs and toxicokinetics information support that cVMS do not biomagnify and that concentrations measured in robust studies in the environment are below toxicity thresholds. Concentrations in the environment are below toxicity thresholds. Traditional measurements used for persistence and biomagnification may not be suitable for cVMSs.

Remarks: The evaluations of the studies on D4 should be considered in the D4 risk assessment. This publication will be consulted during the preparation of the ecologiclal risk assessment for D4.

Short citation (Author, year, or ID)	**FAIRB16A**
Full citation (or link)	**Fairbrother, A., and K.B. Woodburn. 2016. Assessing the aquatic risks of the cyclic volatile methyl siloxane D4. Environmental Science & Technology Letters 3(10): 359-363.**
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature, presenting a review of approaches for aquatic risk assessment**
Study Director (if applicable)	**N/A**
GLP Compliance (if applicable)	**N/A**

Discussion: Article does not present new ecotox data but tabulates existing data. The article explores the challenges with determining D4 toxicity in aquatic species due to its high volatility and low water solubility. Authors report that increased sensitivity occurs when aquatic organisms are tested within artificially closed systems when compared to similar tests conducted in open systems that allow for natural volatilization. The article discusses narcosis mode of action and chemical "activity" (or fugacity) to explain the apparent lack of toxicity of D4 when in environmentally realistic conditions. Concept of "activity" was used in Nusz et al. 2018.

Remarks: This publication will be consulted in the aquatic ecological risk assessment for D4.

Short citation (Author, year, or ID)	**FISK10A**
Full citation (or link)	**Peter Fisk Associates. 2010. Approach to the environmental effects properties of octamethylcyclotetrasiloxane 9D4). Reference code: PFA.151.008.003. August.**
Study type (e.g., OECD Guideline if applicable)	**Written summary of the UK's Environment Agency's 2009 report**
Study Director (if applicable)	**Risk, P.R., A.E. Girling, H.J. Disley, L. McLaughlin, and L.E. Wilmot (authors)**
GLP Compliance (if applicable)	**N/A**

Discussion: This report captures the UK's Environment Agency's 2009 report. The purpose of this report is to set out an approach suitable for REACH, and implement changes reflecting growth of technical knowledge concerning methodology of risk assessment. An approach is set out to understand environmental effects of D4 that is relevant to REACH registration by reviewing the EA 2009 report.

Remarks: The only notable comment states that the study with *Lumbriculus variegatus* with artificial sediment (WILDL09A) is considered less reliable than the study with natural sediment (SPRIN09A).

Short citation (Author, year, or ID)	**WANG13A; BUSER15A**
Full citation (or link)	**Wang, D.G., W. Norwood, M. Alaee, J.D. Byer, and S. Brimble. 2013. Review of recent advances in research on the toxicity, detection, occurrence and fate of cyclic volatile methyl siloxanes in the environment. Chemosphere 93(5): 711-725.** **Buser, A.M. 2015. Corrigendum to Review of recent advances in research on the toxicity, detection, occurrence and fate of cyclic volatile methyl siloxanes in the environment [Chemosphere 93 (5)(2013) 711-725]. Chemosphere 119: 1275-1275.**
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature and corrigendum, WANG13A presents a review of recent advances relating to toxicity, detection and occurrence of cVMSs. The corrigendum, BUSER15A, provides a correction for half-life transformation information for D5.**
Study Director (if applicable)	**N/A**
GLP Compliance (if applicable)	**N/A**

Description: Study is a review article by authors from Environment Canada. No new ecotox information presented. The WANG13A article presents information for D4, D5, and D6 and the fate and behavior of these chemicals in the environment. The article reviewed usage data and patterns of use of these chemicals, and numerous properties related to toxicity, physical chemical data, degradation, partitioning, methods of detections, and environmental concentrations. The article provides recommended physico-chemical properties and most sensitive ecotoxicity values, The article suggests that based on published data reviewed, there is no evidence of trophic biomagnification in aquatic food webs, though some organisms showed a high degree of bioconcentration and bioaccumulation. High concentrations of cVMS in indoor air and biosolids resulted from point sources. Concentrations in water, sediment, and soil were below NOEC values.

Remarks: This publication will be consulted during preparation of the ecological risk assessment for D4.

Short citation (Author, year, or ID)	**HOBSO95A**
Full citation (or link)	**Jobson, J.F. and E. M. Silberhorn. 1995. Octamethylcyclotetrasiloxane (OMCTS), a case study: summary and aquatic risk assessment. Environ. Toxicol. Chem. 14(10):1667-1673.**
Study type (e.g., OECD Guideline if applicable)	**Peer-reviewed literature, presenting a risk assessment approach**
Study Director (if applicable)	**N/A**
GLP Compliance (if applicable)	**N/A**

Discussion: Hobson and Silberhorn (1995) conducted an ecological risk assessment for D4. The effects assessment was based on the results of industry-sponsored aquatic toxicity studies conducted on fish and invertebrates; these are the same studies described previously. Toxicity from aqueous exposure was characterized as requiring extended, continuous exposure and being limited to narcosis-like effects on behavior and survival. The exposure assessment was based on physico-chemical and environmental fate properties, modeling, and monitoring data from four sewage treatment plants. The authors concluded that the concentrations of D4 in aquatic ecosystems are expected to be low and transient in water and sediments. Comparison of predicted surface water concentrations with the lowest NOEC from toxicity studies indicated conservative 64-to 444-fold margins of safety for organisms exposed to the water column and 157- to 1,080-fold margins of safety for benthic organisms. Rapid volatilization and additional dilution in most aquatic environments would increase this margin of safety for aquatic life even further.

Remarks: This article was used in Nusz et al. 2018 as support that D4 exhibits toxicity under the narcosis mode of action.

Short citation (Author, year, or ID)	**REDMA12A**
Full citation (or link)	**Redman, A.D., E. Mihaich, K. Woodburn, P. Paquin, D. Powell, J.A. McGrath, and D.M. Di Toro. 2012. Tissue-based risk assessment of cyclic volatile methyl siloxanes. Environmental Toxicology and Chemistry 31(8): 1911-1919.**
Study type (e.g., OECD Guideline if applicable)	**Peer-reviewed literature, presenting a risk assessment approach**
Study Director (if applicable)	**N/A**
GLP Compliance (if applicable)	**N/A**

Discussion: Article does not present new ecotox data. Article compares measured tissue concentrations of cVMS (including D4) in fish and benthic invertebrates with critical target lipid body burdens (CTLBBs) as estimated with the target lipid model (TLM) to evaluate risk. Analysis included contribution from metabolites to the overall tissue residues using a food chain model calibrated to laboratory and field data. Suggests little evidence for risk of adverse effects of cVMS under present-day emission levels. This model, which resulted in an HC_5 CTLBB of 2.6 µg/mol lipid, was used in the ecological risk evaluation of Nusz et al. 2018.

Remarks: This article was used in Nusz et al. 2018 which is the basis of the ecological risk assessment for D4

Short citation (Author, year, or ID)	**WOODB18A**
Full citation (or link)	**Woodburn, K.B., R.M. Seston, J. Kim, and D.E. Powell. 2018. Benthic invertebrate exposure and chronic toxicity risk analysis for cyclic volatile methylsiloxanes: Comparison of hazard quotient and probabilistic risk assessment approaches. Chemosphere 192: 337-347.**
Study type (e.g., OECD Guideline if applicable)	**Peer reviewed literature discussing risk assessment approaches for benthic invertebrates**
Study Director (if applicable)	**N/A**
GLP Compliance (if applicable)	**N/A**

Description: No new ecotox data presented; data compiled from existing information. Calculated 5th percentile benthic sediment chronic no observed effect concentration (NOEC) fugacity levels. *L variegatus* result of Krueger et al. 2009 determined to be an outlier, used five remaining studies. Sediment concentration data (from field locations worldwide) were expressed as 95% CDF and compared to the invertebrate NOECs using either the HQ or 5% PRA approach. Neither approach resulted in overlap of exposure and effects for D4; thus, there is no risk.

Remark: This publication will be considered in the discussion of risks to benthic invertebrates.

Appendix 3

Supplemental Information for Risk Evaluation for Octamethylcyclotetrasiloxane (D4)

a. Other D4 Assessments

b. Global Monitoring Data

a. Other D4 Assessments

Authorities in Canada, the United Kingdom and Australia have conducted assessments of D4. Those assessments, which reflect the varying chemical regulatory approaches adopted in those countries, and the underlying data are addressed in the draft D4 RE.

- Canada: https://www.canada.ca/en/health-canada/services/chemical-substances/challenge/batch-2/cyclotetrasiloxane-octamethyl.html
- Australia: https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments/tier-ii-environment-assessments/cvms; https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=2031
- UK: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/290565/scho0309bpqz-e-e.pdf

It is also acknowledged that chemical regulatory authorities in the European Union (EU) have conducted certain assessments and initiated certain actions regarding D4 under *Regulation (EU) No 1907/2006* (REACH).

In January 2018, the European Commission issued *Commission Regulation (EU) 2018/35 of 10 January 2018* (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0035&from=EN) that listed D4 in REACH Annex XVII and stipulated that after January 31, 2020, D4 concentration in wash-off cosmetic products on the market must be ≤ 0.1% (by weight) (referred to as "Wash-Off Restriction"). This action was based on a purported determination that D4 met criteria in Annex XIII of REACH for identification as a PBT and vPvB substance and the premise under the EU regulatory approach that any emissions or exposure of such substances are considered to be a "proxy for risk."

In April 2018, industry filed a legal action in the Court of Justice of the European Union (General Court) seeking, among other things, annulment of the Wash-Off Restriction based on various concerns, including that the Commission and ECHA failed to conduct a valid risk assessment and that they failed to conduct or apply a valid weight-of-evidence determination. This matter (Case T-226/18) is still pending before the General Court. See https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1570630612867&uri=CELEX:62018TN0226

In June 2018, the European Chemicals Agency (ECHA) published its decision to add D4 to the list of candidate substances for authorization (Candidate List) as a Substance of Very High Concern (SVHC) in accordance with Article 59 of REACH. This decision was based on ECHA's determination that D4 met the numerical criteria of REACH Annex XIII for PBT and vPvB substances.

In September 2018, industry filed a legal action in the Court of Justice of the European Union (General Court) seeking annulment of the ECHA decision to list D4 as a SVHC based on concerns that ECHA failed to consider all available evidence and properly assess it under

REACH. The matter (Case T-519/18) is still pending before the General Court. See https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1518304338301&uri=CELEX:62018TN0519.

In 2019, ECHA proposed an additional restriction to cover additional uses of D4 (*e.g.*, in leave-on personal care products and other consumer/professional products) (See https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e181a55ade.) Public consultation on the Annex XV report recently ended.

b. Global Monitoring Data

Introduction

Appendix 3b provides information on additional studies that reported D4 concentrations in environmental media including, sediment, surface waters, ambient and indoor air, soil, and biota based on samples collected at locations around the world. These data have been included for completeness, but were not included in the draft D4 RE. During the development of the scope of the D4 ECA, the Agency expressed an interest in generating domestic environmental exposure data to support an assessment of the risks to sediment and aquatic-dwelling organisms in the United States from exposure to D4 from domestic sources of the substance. Consequently, those data were used in the draft D4 RE.

1 Outdoor Air

- USA / Canada

Concentrations of D4 in air were found to be positively correlated with population density (Yucuis et al., 2013), with concentrations increasing from a rural area, to suburban, and to an urban center. Mean concentrations of D4 were 9.88, 18.5, and 64.4 ng/m^3 in the rural, suburban, and urban areas, respectively.

Passive air samplers were deployed in the Toronto, Ontario area from July until October 2012 as part of a study to calibrate and evaluate the use of XAD-PUFs for use in measuring cVMS materials in air (Krogseth et al., 2013a). The samplers were deployed at 26 sites, ranging in terms of population density and proximity to WWTPs. Levels of D4 were below the LOD or LOQ at five sites, including the three rural locations. At the two sites within a WWTP, levels of D4 were outside the upper range of the calibration curve. For comparison, active air samplers were deployed at the University of Toronto. The mean (± st dev) concentration of D4 determined in those samples was 24.2 ± 19.1 ng/m^3.

Cheng et al. (2011) measured concentrations of D4 of 800-1270 ng/m^3, 2000-2110 ng/m^3 and 378-432 ng/m^3 in air samples collected above the primary clarifier, aeration tank, and secondary clarifier, respectively, at an Ontario wastewater treatment plant (WWTP) over the period July to September 2009. Levels upwind and downwind of the plant were 101 to 153 ng/m^3 (mean value 131; N = 3) and 39.8 ng/m^3 (N = 1), respectively. Concentrations of D4 in two air samples collected in November 2009 above the aeration tank of a second Ontario WWTP were 231 and 250 ng/m^3. The same study also measured air concentrations of D4 of 471 and 1840 ng/m^3 at two sites located downwind of two Ontario landfills. Concentrations of D4 upwind of the landfills were 70.1 and 154 ng/m^3. Sampling for the landfill sites occurred from June to August 2009.

Another study conducted in the Toronto, Ontario area collected air samples at a semi-urban meteorological station from March 2010 to April 2011 (Ahrens et al., 2014). Sampling was done using both passive and active air samplers. Concentrations of D4 in air samples collected with passive air samplers (N=12) ranged from 9.3 to 35 ng/m^3, with a mean value of 21 ± 8.3 ng/m^3 and a median value of 18 ng/m^3. Concentrations of D4 in air samples collected using active air samplers (N = 70) ranged from 2.8 to 77 ng/m^3, with a mean value of 16 ± 12 ng/m^3 and a median value of 14 ng/m^3.

Emissions to air were assessed at eight WWTPs around Ontario, Canada (Shoeib et al., 2016). Passive air samplers were deployed on-site above the active tank and off-site for comparison. Sampling campaigns were conducted during summer 2013 (August to November) and winter 2014 (January to March). In the summer, concentrations of D4 ranged from 31.0 to 393 ng/m^3 and 39.6 to 343 ng/m^3 at the off-site and on-site locations, respectively. In the winter, concentrations of D4 ranged from 104 to 373 ng/m^3 and 140 to 348 ng/m^3 at the off-site and on-site locations, respectively.

A pilot study within the Global Atmospheric Passive Sampling (GAPS) network was conducted to examine the global distribution of volatile methyl siloxanes in the atmosphere. This study included 20 locations worldwide, ranging from sites in the Arctic to remote background locations, to urban areas. D4 was detected in samples from 11 of the 12 background sites (Kosetice, Czech Republic; Whistler, BC; Tudor Hill, Bermuda; Storhofdi, Iceland; Malin Head, Ireland; Cape Grim, Tasmania; Fraserdale, ON; Ucluelet, BC; Point Reyes, CA; Hilo, HI; Groton, CT) at concentrations in air ranging from 0.94 to 45 ng/m^3. Detectable concentrations of D4 were found in air samples from all three urban sites, with concentrations ranging from 5.4 to 50 ng/m^3, and a concentration of 2.6 ng/m^3 was found at the one agricultural site. Concentrations of D4 were also detected at all four Arctic sites, ranging from 0.66 to 18 ng/m^3 (Genualdi et al. 2011).

An additional two years (2013 and 2015) of sampling were conducted within the GAPS network (Rauert et al., 2018). Detectable concentrations of D4 were found in air samples from all three urban sites, with concentrations ranging from 22 to 76 ng/m^3, and a concentration of 23-100 ng/m^3 was reported at the one agricultural site. Concentrations of D4 were also detected at all four Arctic sites, ranging from 1.6 to 131 ng/m^3. Concentrations of D4 at the background sites ranged from 0.8 to 145 ng/m^3.

- Europe

Air sampling was conducted at the Zeppelin research station in Svalbard, Norway, which is considered a remote location, and at Birkenes, Norway, located in southern Norway (Bohlin-Nizzetto et al., 2019). The weekly sampling at Zeppelin aimed to better assess the seasonal variability and a better coverage of the levels in the Arctic. The monthly sampling at Birkenes aimed to assess seasonal variability of D4 and the influence of vicinity to source regions. All samples were collected Friday-Monday in order to minimize the risk of contamination from activities at the stations during weekdays. The range and mean concentration of D4 at Zeppelin and Birkenes were 0.09-1.0 ng/m^3 (0.04 ng/m^3) and 0.2-0.9 ng/m^3 (0.6 ng/m^3), respectively.

Passive air samplers were deployed in 2018 at five locations around Oslo, Norway and remained in the field for three months (Heimstad et al., 2019). Concentrations of D4 ranged from 19.5 to 53.2 ng/m^3 (mean value 30.8 ng/m^3).

Passive air samples were collected from along the Kucuk Menderes River, located in southwestern Turkey (Yaman et al., 2019). The river catchment includes agricultural, residential, and industrial areas. Passive air samplers loaded with XAD-2 resin were deployed at 10 sites along the river for a two-week sampling period. Concentrations of D4 in the surface ranged from 7.6 to 58.3 ng/m^3. The mean concentration of D4 in the surface water samples was 17.6 ± 15.7 ng/m^3.

In Spain, an air monitoring study evaluated outdoor air in ten Catalan urban areas with different industrial impacts (Gallego et al., 2017). Several different sampling campaigns were carried out between 2013 and 2015, collected a total of 271 samples. Mean concentrations of D4 at each sampling area ranged from 9 to 676 ng/m^3.

Passive air samplers were deployed in an urban area and a remote area of Portugal as part of a method validation study for the determination of D4 in air (Ramos et al., 2016). XAD-4 impregnated SIPs were deployed for 3 months. In addition, pine needles were collected from each site to determine if they could also serve as passive samplers for airborne contaminates. Samples from the urban area and the remote area had levels of D4 of 583 ng_{SIP} and 35.4 ng_{SIP} in the air samplers and concentrations of D4 of 1.3 ng/g dw and 0.40 ng/g dw in the pine needles, respectively. These techniques were employed for a larger scale study that collected samples from urban areas (N=2), industrial parks (N=2), beach resorts (N=2), and remote areas of Portugal (Ratola et al., 2016). In air samples (N=32), concentrations of D4 ranged from 0.6 to 7.8 ng/m^3, with D4 contributing a mean of 21% of the total concentration. Concentrations of cVMS in pine needles ranged from 2 to 118 ng/g dw, with D4 contributing approximately 3% to the total concentration. These results were generated using a QuEChERS methodology.

Kierkegaard and McLachlan (2013) conducted air sampling on the outskirts of the small village of Tystberga, Sweden, located approximately 70 km southwest of Stockholm. Samples were collected from passive air samplers daily over a six-week period between 4 November and 14 December 2011. Concentrations of D4 ranged from 1.8 to 8.0 ng/m^3 (mean value 3.5 ng/m^3). The authors noted that the concentrations of D4 may have been overestimated as a result of possible conversion of other cyclic volatile methylsiloxanes on the cartridge sorbent.

The occurrence of D4 in Arctic air was investigated by Krogseth et al. (2013b) by conducting air sampling at the Zeppelin observatory, which is located close to the Ny Ålesund settlement in the Svalbard archipelago. Two sampling campaigns were conducted: one in late summer (August – October) and one in early winter (November – December) 2011. Concentrations of D4 ranged from ND to 2.20 ng/m^3 in summer, and from ND to 2.13 ng/m^3 in winter. The authors noted that the concentrations of D4 may have been overestimated as a result of possible conversion of other cyclic volatile methylsiloxanes on the cartridge sorbent.

Between March and April 2011, air samples were collected at the university campus area in the city of Barcelona, Spain (Companioni-Damas et al., 2014). Mean concentrations of D4 in the air collected at these two locations ranged from 73 to 79 ng/m^3.

Air samples were collected during 2004 and 2005 from several Nordic countries, including Denmark, Faroe Islands, Finland, Iceland, Norway, and Sweden (Kaj et al., 2005a). Concentrations of D4 in these air samples ranged from 80 to 4,000 ng/m^3 (N=24). The greatest concentrations of D4 were observed in samples collected from WWTPs and in urban centers.

In 2004, air samples were collected from sites in Sweden ranging from background areas to those with potential point sources of emission (Kaj et al., 2005b). Concentrations of D4 in the collected air samples ranged from 18 to 300 ng/m^3 (N=11).

- <u>Asia</u>

In January and July of 2017, air samples (N=40) were collected from 10 sites around Dian Lake in southwestern China (Guo et al., 2019a). Air was pumped through ENV+ cartridges at a rate of

2 L/min for a collection time of 24 h. Mean concentrations of D4 in air samples collected in January (winter) and July (summer) were 13.4 ± 4.9 ng/m^3 and 5.38 ± 3.13 ng/m^3, respectively.

Air samples were collected at three construction sites, one automobile plant, two paint factories, 21 factory dormitories (two from each construction site and five from other plants), 20 residential properties and 10 offices located in southwestern China, from January to March, 2017 (Guo et al., 2019b). The greatest outdoor air concentration of D4 was observed near the automobile plant, with an approximate air concentration of 1.0x10^5 ng/m^3. Concentrations of D4 ranged from 16 to 26 ng ng/m^3 (detection frequency of 60%) in outdoor air samples from residential properties.

At a rural site located approximately 60 km northwest of Tokyo, Japan, sampling was conducted one day per week over a period of one year (February 2014 – February 2015) (Horii et al., 2016). The mean concentration of D4 in the collected air samples was 123 ng/m^3, with a range of 11 to 567 ng/m^3.

Passive air samplers were deployed at several sites, ranging from densely populated cities to more remote areas, across the Tibetan Plateau (Wang et al., 2018). The samplers were deployed from early May to late July, 2013. Concentrations of D4 ranged from 6.1 to 96.6 ng/m^3, with a mean concentration of 38.8 ng/m^3.

Results of a siloxane air monitoring study were published by Horii et al. (2018), but the study could not be summarized here as it is published in Japanese.

Air samples were collected from three locations around Harbin, China; one site was inside of a local WWTP, one was 500 m away from the WWTP, and the third was in the urban center of Harbin (Li et al., 2016). Samples were collected from each site in January, April, July, and October of 2012. For three consecutive days during each sampling campaign, on each day one air sample was collected within 23 h. Concentrations of D4 were greatest in the air samples collected from within the WWTP, ranging from 5.6 to 125 ng/m^3, with a mean concentration of 56.4 ng/m^3. In air samples collected from the site near the WWTP, concentrations of D4 ranged from <LOD to 27.4 ng/m^3, with a mean concentration of 15.3 ng/m^3. Air samples collected from the urban center had concentrations of D4 ranging from <LOD to 4.7 ng/m^3, with a mean concentration of 3.9 ng/m^3.

Air samples were collected from Guangzhou, Macau, and Nanhai in the Pearl River Delta, South China (Wang et al., 2001). In Guangzhou, samples were collected on 10 July 1996 from a variety of different areas around the city. Mean concentrations of D4 in the air of urban mixed areas, industrial area, landfill, WWTP, suburban, and a forest park were 900 ng/m^3, 13,500 ng/m^3, 11,400 ng/m^3, 10,300 ng/m^3, 400 ng/m^3, and non-detect, respectively. In Macau, samples were collected on 20 November 1995. Mean concentrations of D4 in the air of an urban area, a local university, and a nearby beach were 3,000 ng/m^3, 2,500 ng/m^3, and 250 ng/m^3, respectively. Samples were collected in Nanhai on 10-12 July 1996, from sites ranging from towns with small factories or manufacturers to an agricultural region. The mean concentration of D4 in samples from Nanhai was 900 ng/m^3.

- South America

To address a data gap in atmospheric monitoring data from developing regions, passive air samplers were deployed at sites throughout the Group of Latin American and Caribbean countries (GRULAC) in 2015 (Rauert et al., 2018b). Sites included urban, background, and agricultural areas. At the urban site of Rio Gallegos, Argentina, the concentration of D4 was 36 ng/m^3. At the background sites (N = 4), concentrations of D4 ranged from 8.0 to 42 ng/m^3. The concentration of D4 at the agricultural site (Sonora, Mexico) was 8.7 ng/m^3.

- USA / Canada

In November 2014, air concentrations of D4 were determined in a classroom at the University of California, Berkeley, California (Tang et al., 2015). Monitoring was done on five days during a total of 19 classes when room occupancy was equal to or greater than 17 occupants. Concentrations of D4 in the classroom air ranged from 300 to 3,900 ng/m^3, with a mean of 1,100 ng/m^3.

- Europe

Passive air samplers were deployed in three buildings on the Ultuna campus of the Swedish University of Agricultural Sciences in Uppsala, Sweden in September to November 2016 (Sha et al., 2018). Sampling areas included a computer room, dining areas (N=3), laboratories (N=3), lecture rooms (N=3), offices (N=8), and homes (N=9). D4 was detected in 93% of the samples collected. The concentration of D4 in the air of the computer room was 110 ng/m^3, and mean concentrations of D4 in the air of the dining areas, laboratories, lecture rooms, and offices were 170 ng/m^3, 24 ng/m^3, 120 ng/m^3, 280 ng/m^3, and 240 ng/m^3, respectively.

Indoor air sampling campaigns were conducted from May to August 2011 in Italy and the United Kingdom (Pieri et al., 2013). Air samples were collected from eight types of indoor environments. In private residences, air was collected in bathrooms (N=18), living rooms (N=13), adult- (N=10), boy- (N=11), and girl- (N=12) rooms. In settings with expected different diurnal occupancy patterns such as schools (N=5), supermarkets (N=10), and offices (N=12), samples were collected during hours that represent typical exposure. Air samples were collected by pumping 5 L of air through sorbent tubes containing Tenax GR (35/60 mesh) and Graphitized Carbon Black. In indoor environments in Italy, mean concentrations of D4 ranged from 2.2 to 27 ng/m^3. In indoor environments in the UK, mean concentrations of D4 ranged from 6.9 to 68 ng/ m^3. In both countries, the highest mean concentrations of D4 in indoor air were observed in the bathroom.

In Barcelona, Spain, indoor air samples were collected between March and April 2011 from offices, laboratories, and apartment homes (N=2 of each environment) (Companioni-Damas et al., 2014). Air samples were collected by pumping 2,700 L of air over Isolute ENV+ SPE cartridges, at a rate of 1.5 L/min. Mean concentrations of D4 in offices, laboratories, and homes ranged from 226 to 416 ng/m^3, 641 to 833 ng/m^3, and 1592 to 3052 ng/m^3, respectively.

- Asia

Indoor air and dust samples were collected from 24 hair salons in Hanoi, Vietnam (Tran et al., 2018). Air samples were collected from 20 to 24 using a low pump. Concentrations of D4 in the air samples ranged from 86.5 to 605 ng/m^3, with a median value of 205 ng/m^3 and a mean value

of 243 ng/m^3. Dust samples were collected using a broom on the floor and furniture surfaces in the hair salons. Concentrations of D4 in the dust samples ranged from 35.3-322 ng/g, with a median value of 101 ng/g and a mean value of 121 ng/g.

Indoor air and dust samples were collected at three construction sites, one automobile plant, two paint factories, 21 factory dormitories (two from each construction site and five from other plants), 20 residential properties and 10 offices located in southwestern China, from January to March, 2017 (Guo et al., 2019b). The greatest indoor air concentration of D4 was observed in the automobile plant, with an approximate air concentration of 5.0x10^5 ng/m^3, while the greatest concentration of D4 in dust was collected from one of the paint factories (approximately 6,000 ng/g). Factory dormitories were also sampled and the greatest concentration of D4 in air and dust were approximately 8.0x10^4 ng/m^3 and 2,000 ng/g, respectively. Concentrations of D4 ranged from 330 to 2,100 ng/m^3 (detection frequency of 80%) in indoor air samples from residential properties, which were comparable to those collected from offices.

Indoor air samples were collected from September 2016 to January 2017 from different indoor environments in four cities in northern Vietnam (Tran et al., 2017). In Hanoi, sampling locations included homes (N=19), car interiors (N=8), offices (N=9), kindergartens (N=7), laboratories (N=19), and hair salons (N=13). For other cities, air samples were only collected from homes: Bacninh (N=8), Thaibinh (N=6), and Tuyenquang (N=8). The most common room sampled in homes was the living room. Air samples were collected for 12 – 24 h. Concentrations of D4 in the air samples ranged from non-detect to 662 ng/m^3 (detection frequency of 87.5%), with a median value of 13.4 ng/m^3 and a mean value of 51.4 ng/m^3. The greatest concentration of D4 in indoor air were found in the hair salons.

Between January and March 2012, samples of indoor air and dust were collected industrial locations in China (Xu et al., 2015). Seven different industrial facilities were sampled (2 construction sites, 2 paint production plants, 1 automobile plants, 1 engine plant, and 1 textile plant). Active air samplers pumped air through ENV+ sorbent cartridges to collect a sample. Dust was collected using vacuum cleaners and brushes. In addition, 60 paired indoor air and floor dust samples were collected in residential areas. In indoor air collected from residences, D4 was detected in 67% of the samples collected. D4 was also detected in indoor dust collected from residences, but individual oligomer concentration data were not reported in the manuscript. Indoor air and dust samples collected from the industrial facilities had concentrations of cVMS that were approximately 1-3 orders of magnitude greater than those from residences. D4 was a prominent oligomer in the industrial air samples. The greatest concentration of D4 was observed in the automobile plant, with a concentration of approximately 5.0x10^5 ng/m^3.

Air samples (N=35) were collected August to October, 2011, from an area of Shandong Province, China that has siloxane production facilities, an area downwind of that production area, and an area considered to represent background levels (Xu et al., 2012). The mean concentration of D4 in indoor air of the industrial facilities was 2.7x10^6 ng/m^3. Concentrations of D4 in outdoor air and soil decreased with increased distance from the siloxane production area. In indoor air from residences located in the background area, concentrations of D4 ranged

from 180 to 310 ng/m^3, with a detection frequency of 67%. The mean concentration of D4 in indoor dust collected from residencies within the background area was 23.3 ng/g, with a detection frequency of 67%.

- USA / Canada

In April 2014, surface water samples were collected from Big Thompson River and Fossil Creek Ditch, both of which receive wastewater effluents in the area of Fort Collins, Colorado (Zhang, 2014). Samples were collected at points 1 m, 10 m, and 50 m from discharge points. D4 was not detected in any of the collected surface water samples.

Surface water samples were collected from areas receiving wastewater effluent at eleven sites located in Ontario and Quebec. Samples were collected between May and October 2010. Concentrations of D4 ranged from <9.0-23 ng/L (Wang et al 2013).

- Europe

Surface waters were collected from the Kucuk Menderes River, located in southwestern Turkey (Yaman et al., 2019). The river catchment includes agricultural, residential, and industrial areas. Grab samples of surface water were collected from 10 sites along the river. Concentrations of D4 in the surface ranged from 5.96 to 33.4 ng/L. The mean concentration of D4 in the surface water samples was 17.7 ± 8.8 ng/L.

Surface water samples were collected from Catalonia (NE Spain) in 2011 from Llobregat River (N = 3) and the Riera de Rubí (N = 3) (Sanchís, et al., 2013). Sampling locations were in the vicinity of WWTP discharges. Concentrations of D4 ranged from 61.2 to 987 ng/L in the water samples (reported MLOQ = 26 ng/L).

An additional study analyzed surface waters collected from rivers in the Barcelona region in May 2011 for concentrations of D4 (Companioni-Damas et al., 2012a). Grab samples were collected from the Llobregat River (N=7) and Besós River (N=5), which run through very densely populated and industrialized areas, receiving extensive urban and industrial wastewater discharges from more than 3 million inhabitants. Concentrations of D4 were below the LOD (6 ng/L) in all samples collected.

In 2006, surface waters were collected from the Inner and Outer Oslofjord, Norway (Schlabach et al., 2007). Concentrations of D4 in all surface water samples (N=4) were below the LOD (30 ng/L).

Surface water samples were collected during 2004 and 2005 from several Nordic countries, including Denmark, Iceland, Norway, and Sweden (Kaj et al., 2005a). Concentrations of D4 in these surface water samples (N=14) were all below their respective LODs, which ranged from 40 to 90 ng/L

In 2004, surface water samples were collected from sites in Sweden ranging from background areas to those with potential point sources of emission (Kaj et al., 2005b). Concentrations of D4

in the collected surface samples were all below their respective LODs, which ranged from 60 to 80 ng/L (N=26).

- Asia

In January and July of 2017, surface water samples (N=20) were collected from 10 sites around Dian Lake in southwestern China (Guo et al., 2019a). Mean concentrations of D4 in surface water samples collected from Dian Lake in January (winter) and July (summer) were 11.8 ± 6.4 ng/L and 9.8 ± 4.9 ng/L, respectively. Surface water samples were also collected from seven rivers near the point where they flow into Dian Lake. Mean concentrations of D4 in surface water samples collected from the Inflow Rivers in January (winter) and July (summer) were 18.3 ± 1.6 ng/Land 17.1 ± 1.9 ng/L, respectively.

Zhi et al. (2018), conducted a study of paired surface water and sediment samples from lake in the crude oil production areas of Daqing, Heilongjiang Province, China. Sampling areas included newly developed oilfields (N=8), long-established oilfields (N=25), and reference areas located far away from the dense oilfield area. In surface waters from the reference area, D4 was detected in 50% of the surface water samples, with concentrations ranging from <LOQ – 39.7 ng/L. The median and mean concentration of D4 in the reference area surface water samples was 5.10 ng/L and 10.4 (± 14.1) ng/L, respectively. In surface waters from the new oilfield area, D4 was detected in 25% of the surface water samples, with concentrations ranging from <LOQ – 13.7 ng/L. The median and mean concentration of D4 in the new oilfield area surface water samples was <LOQ and 1.85 (± 4.80) ng/L, respectively. In surface waters from the old oilfield area, D4 was detected in 44% of the surface water samples, with concentrations ranging from <LOQ – 36.5 ng/L. The median and mean concentration of D4 in the old oilfield area surface water samples was <LOQ and 5.50 (± 9.40) ng/L, respectively.

Surface water samples (N=13) were collected from Dongting Lake, the second largest freshwater lake in China, in October 2016 (Zhang et al., 2018). Concentrations of D4 ranged from 6.07 to 85.6 ng/L, with mean and median concentrations of 48.2 ng/L and 48.8 ng/L, respectively.

D4 was detected in water samples (N = 9) collected from the Ara, Tama, and Yoro rivers, which all flow into Tokyo Bay, Japan (Horii, et al., 2013). Concentrations of D4 ranged from 2.9 to 16 ng/L (mean value 6.4 ng/L). Sampling was conducted between October and November, 2012.

In a related study, surface water samples were collected from six major rivers which flow into Tokyo Bay (Ara River, Sumida River, Edo River, Yoro River, Tama River, and Tsurumi River) (Horii et al., 2017). The sampling campaign was conducted from October 2012 to April 2013. A total of 48 river water samples were collected. D4 was detected in 94% of the collected samples, with concentrations ranging from <0.9 to 140 ng/L and a mean concentration of 13 ng/L.

4 Sediment

- USA / Canada

Surface sediments sampled in 2010 from 11 locations adjacent to WWTP discharge sites in southern Ontario and southern Quebec, Canada, had concentrations of D4 ranging from <3.0 to 49 ng/g dw (Wang et al. 2013).

As part of a long-term monitoring program being conducted in Lake Ontario, surface sediments were collected at five locations, two within Lake Ontario and three within Hamilton Harbor (Kim 2018a). Samples were collected annually from 2011 through 2016. Concentrations of D4 in sediment from the Lake Ontario sites were less than the method detection limit. In sediments collected at the sites within Hamilton Harbor, mean concentrations of D4 ranged from 3.10 to 17.7 ng/g dw.

Surface sediments were also collected during the long-term monitoring program conducted in Lake Pepin, Minnesota (Kim 2018b). Surface sediments were collected annually from 2011 through 2016 along a transect that bisects the lake. Concentrations of D4 in the collected sediments were below the method detection limit.

In 2007, sediment was collected from Lake Opeongo, Ontario and analyzed for cVMS (Powell 2010). Concentrations of D4 were less than the method detection limit.

Surface sediments and sediment cores were collected from Lake Ontario in 2006 (Powell and Kozerski 2007). Surface sediments from Toronto Harbor contained the greatest levels of D4, with a concentration of 290 ng/g dw. In contrast, the concentrations of D4 were less than the analytical method detection limit (6.0 ng/g dw) in the surface sediments and sediment cores from the four sedimentary basins, which included Kingston, Rochester, Mississauga, and Niagara Basins.

- Europe

In the autumn of 2018, the Norwegian Institute for Water Research (NIVA) collected a sediment sample from one station within the Inner Oslofjord (Ruus et al., 2019). D4 was not detected in this sediment sample.

As part of a long-term monitoring program being conducted in Inner Oslofjord, Norway, surface sediments were collected at five locations (Kim 2018c). Samples were collected annually from 2011 through 2016. Mean concentrations of D4 in sediment collected from Inner Oslofjord ranged from 0.18 to 19.2 ng/g dw. Many samples had concentrations of D4 that were below the MDL, including the minimum concentration reported here, but uncensored values were listed in the report.

Sediment samples were collected from Catalonia (NE Spain) in 2011 from Llobregat River (N = 3) and the Riera de Rubí (N = 3) (Sanchís, et al., 2013). Concentrations of D4 in sediment ranged from <MLOQ to 679 ng/g dw (reported MLOQ = 1.8 ng/g ww).

Sediments were collected in November 2010 and April 2011 near Tromsø, Norway (Warner et al., 2014). During each sampling campaign, the surface 0-2 cm of sediment was collected from a harbor near Tromsø and from a more remote location. Concentrations of D4 were below the MDL (2.4 ng/g ww) in all sediment samples collected.

Samples of sediment were collected from six locations within the Humber Estuary, off the east coast of England, in September and October 2009 (Kierkegaard et al., 2011). A stainless-steel spoon was used to collect the top layer (1-2 cm) of undisturbed sediment. Concentrations of D4 in the sediment were less than 1-2 ng/g dw, which was below the LOQ.

In July 2009, sediments were collected from Adventfjorden and Kongsfjorden, on the Norwegian archipelago of Svalbard (Warner et al., 2010). Sediments (surface 2 cm) were collected following a transect extending from wastewater effluent outfalls, with the nearest sampling location being 50 m away and 90 m away in Adventfjorden and Kongsfjorden, respectively. Concentrations of D4 in all sediment samples collected were below the MDL (0.9 ng/g ww).

In the Norwegian Arctic, D4 was not detected (reported detection limit 1.1-4.8 ng/g dw) in five surface sediment (0-2 cm) samples collected around Svalbard in 2008 and in Lake Ellasjøen on Bjørnøya in 2004 (Evenset et al., 2009).

In 2006, surface sediments were collected from the Inner and Outer Oslofjord, Norway (Schlabach et al., 2007). Concentrations of D4 in all surface sediment samples (N=6) were below their respective LODs (4- 38 ng/g dw).

Sediments were collected in 2003 through 2005 from locations throughout several Nordic countries, including Denmark, Faroe Islands, Finland, Iceland, Norway, and Sweden (Kaj et al., 2005a). A sediment sample with a concentration of D4 of 84 ng/g dw was the only one of the 24 sediment samples collected with a concentration of D4 above the LOD. This sample was collected near Roskilde, Denmark.

In 2004, sediment samples were collected from sites in Sweden ranging from background areas to those with potential point sources of emission (Kaj et al., 2005b). Concentrations of D4 in the collected sediment samples were all below their respective LODs, which ranged from 6.9 to 115 ng/g dw (N=27).

- <u>Asia</u>

In January and July of 2017, surface water samples (N=20) were collected from 10 sites around Dian Lake in southwestern China (Guo et al., 2019a). Mean concentrations of D4 in surface water samples collected from Dian Lake in January (winter) and July (summer) were 16.4 ± 6.1 ng/g dw and 9.7 ± 2.9 ng/g dw, respectively.

As part of a long-term monitoring program being conducted in Tokyo Bay, Japan, surface sediments were collected at 20 locations (Kim 2018d). Samples were collected annually from 2011 through 2016. The 20 sampling locations were grouped into 4 sections, based on their proximity to the most urbanized areas (increase in number indicates an increase in distance). Mean concentrations of D4 in sediment collected from Section 2, Section 3, Section 4 and Section 5 ranged from 9.27 to 24.2 ng/g dw, 11.6 to 43.3 ng/g dw, 4.18 to 34.4 ng/g dw, and 0.80 to 1.99 ng/g dw, respectively.

From March to April 2016, coastal sediment samples were collected from bays in the southeastern maritime industrial region of South Korea, which represent the most heavily industrialized bays in South Korea (Lee et al., 2019). A total of 69 surface sediments (0-5 cm) were collected. Concentrations of D4 in these surface sediments ranged from non-detect to 86.0 ng/g dw, and were detected in 99% of the samples. The median and mean concentration of D4 in the sediment samples was 3.34 and 5.80 (± 11.3) ng/g dw, respectively.

Sediment samples (N=13) were collected from Dongting Lake, the second largest freshwater lake in China, in October 2016 (Zhang et al., 2018). Concentrations of D4 ranged from 3.98 to 360 ng/g dw, with mean and median concentrations of 54.4 ng/g dw and 26.7 ng/g dw, respectively.

Zhi et al. (2018), conducted a study of paired surface water and sediment samples from lake in the crude oil production areas of Daqing, Heilongjiang Province, China, in November 2015. Sampling areas included newly developed oilfields (N=8), long-established oilfields (N=25), and reference areas located far away from the dense oilfield area. In sediments from the reference area, D4 was detected in 50% of the sediment samples, with concentrations ranging from <LOQ – 12.3 ng/g dw. The median and mean concentration of D4 in the reference area sediment samples was 1.78 ng/g dw and 3.48 (± 4.49) ng/g dw, respectively. In sediments from the new oilfield area, D4 was detected in 38% of the sediment samples, with concentrations ranging from <LOQ – 30.8 ng/g dw. The median and mean concentration of D4 in the new oilfield area sediment samples was <LOQ and 8.18 (± 12.0) ng/g dw, respectively. In sediments from the old oilfield area, D4 was detected in 80% of the sediment samples, with concentrations ranging from <LOQ – 74.6 ng/g dw. The median and mean concentration of D4 in the old oilfield area sediment samples was 19.0 and 26.2 (± 24.2) ng/g dw, respectively.

Sediment was collected near seven coastal cities of the Bohai Sea, China in September 2015 (Zhi et al., 2019). Sediment samples consisted of the top 0-5 cm of surface sediment, collected with a bucket grab sampler. Concentrations of D4 in these sediments ranged from 14.9 to 39.8 ng/g dw.

Surface sediment samples (0-4 cm depth) were systematically collected at 42 locations in November 2014 from industrialized bays around Korea (Lee et al., 2018). D4 was detected in 95% of the surface sediment samples, with concentrations ranging from <LOQ – 335 ng/g dw. The median concentration of D4 in surface sediment samples was 5.17 ng/g dw. In addition, a sediment core was collected from Ulsan Bay, Korea, in July 2015. D4 was detected in 58% of the sediment core samples.

D4 was detected at only trace levels or below the method detection limit (17 ng/g ww) in sediment samples (N = 9) collected from the Ara, Tama, and Yoro rivers, which all flow into Tokyo Bay, Japan (Horii et al., 2013). Sampling was conducted between October and November, 2012.

In 2009, sediment samples were collected downstream of major cities and tributaries of the Songhua River in China (Zhang et al., 2011). Concentrations of D4 in sediments ranged from 0.98 to 33.0 ng/g dw (N=25). D4 was detected in 100% of the sediments collected. The median and mean concentration of D4 in the collected sediment samples was 5.47 ng/g dw and 7.23 (±6.93) ng/g dw, respectively.

- USA / Canada

From November 2013 to May 2014, samples of sludge were collected from the City of Loveland Wastewater Treatment Plant, Loveland, Colorado and the Drake Wastewater Reclamation Facilities in Fort Collins, Colorado (Zhang, 2014). Concentrations of D4 in influent and effluent ranged from 700 to 11,300 ng/L and from 700 to 6,400, respectively.

In 2012, influent and effluent were collected from two WWTPs, one serving a population of approximately 60,000 people and the other serving a population of approximately 380,000 people (Knoerr et al., 2017). The mean concentration of D4 in influent from each WWTP was 180 ng/L. Concentrations of D4 in effluent from each WWTP were less than site-specific detection limits.

Eleven WWTPs from southern Ontario and southern Quebec sampled in 2010 had D4 concentrations ranging from 282 to 6,690 ng/L and <9.0 to 45 ng/L in influent and effluent, respectively (Wang et al. 2013). Mean removal efficiency of D4 was found to be 98% (Wang et al. 2013). At a municipal WWTP discharging to Lake Ontario, mean concentrations of D4 were 166-1,130 ng/L in the influent and <9.0-26 ng/L in the final effluent, measured in winter of 2011 (Wang et al. 2015a).

- Europe

Effluent was collected from the Bekkelaget Sewage Treatment Plant located in the greater Oslo, Norway area in June 2018 using fixed equipment to collect a 24 h sample (Ruus et al., 2019). D4 was not detected in the collected effluent.

As part of a method development study, samples of water were collected from a water purification plant (Murcia, Spain), a river water sample (Alcoy, Spain), wastewater samples from three different points of Rincón de León WWTP (three samples, WWTP1) (Alicante, Spain), from Monte Orgegia WWTP (one sample, WWTP2) (Alicante, Spain), and from a WWTP in Portugal (one sample) (Costa dos Reis et al., 2018). D4 was present in the sample from the Portuguese WWTP, at a mean concentration of 3,100 ng/L. It is not reported whether this was influent or effluent.

Influent and effluent were collected during seven consecutive days in April 2012 from a municipal WWTP in Athens, Greece that serves a population of approximately 3,700,000. These samples were collected as 24-hour flow-proportional composite samples. Concentrations of D4 in influent ranged from 99 to 187 ng/L (N =7), with a mean value of 149 ng/L. In effluent, concentrations of D4 ranged from 103 to 197 ng/L (N = 7), with a mean value of 129 ng/L (Bletsou et al., 2013).

Passive samplers were deployed in the effluent channel of the Budds Farm WWTP in Havant, United Kingdom, which serves a population of approximately 400,000 (Bruemmer et al.,2015).

Samplers were deployed over the dates of 6-13 March 2012. The mean (± st dev) concentration of D4 in effluent samples was 50± 35 ng/L (N=16). Concentrations of D4 in effluent samples ranged from 15 to 152 ng/L.

Sanchís, et al. (2013) collected 24-hour integrated samples from numerous WWTPs in Catalonia (NE Spain) during February 2011. Influent was collected from 15 sites and the concentrations of D4 ranged from <26 to 1,089 ng/L, with a detection frequency of 86.7%. Median and mean concentrations of D4 in influent were 210 ng/L and 324ng/L, respectively. Effluent was collected from 16 sites and D4 was detected in effluent from 13 sites, with concentrations of D4 ranging from <26 to 476 ng/L and a detection frequency of 75%. Median and mean concentrations of D4 in effluent were 18.9 ng/L and 76.0 ng/L, respectively.

At a municipal WWTP in Wellingborough, United Kingdom, influent and effluent were collected on 22/23 March 2010 and 07/08 July 2010 (van Egmond et al., 2013). Samples were collected using an autosampler, which collected a sample every 90 minutes for a total of 22.5 h. Concentrations of D4 in the influent were generally below the LOQ (200 ng/L), with only two of eight samples exceeding the LOQ (220 and 300 ng/L). In effluent samples, concentrations of D4 were all below the LOQ (10 ng/L).

In 2006, influent and effluent were collected from the Bekkelaget and VEAS Sewage Treatment Plants located in the greater Oslo, Norway area (Schlabach et al., 2007). Concentrations of D4 in the influent and effluent ranged from 100-200 ng/L and from <30 – 100 ng/L, respectively.

Samples of various process waters were collected during 2004 and 2005 from several Nordic countries, including Denmark, Faroe Islands, Finland, Iceland, Norway, and Sweden (Kaj et al., 2005). Effluent of eight different WWTPs was collected. Concentrations of D4 in seven of the effluent samples were below their respective LODs (ranging from 60 to 80 ng/L), and one sample from Finland had a concentration of 110 ng/L. Influent of five different WWTPs was collected. Concentrations of D4 in the influent samples ranged from <300 ng/L to 3,700 ng/L. This maximum concentration was observed in influent that received wastewater from an industrial facility. In addition, leachate was collected from ten landfills. Concentrations of D4 in nine of the leachate samples were below their respective LODs (ranging from 40 to 120 ng/L), and one sample from Iceland had a concentration of 1,100 ng/L

- Asia

Effluent was collected from six oilfield combination stations in the crude oil production areas of Daqing, Heilongjiang Province, China (Zhi et al., 2018). Of the six samples collected, D4 was detected in two samples, with concentrations of 35.7 ng/L and 219 ng/L.

Lan et al. (2019) studied the seasonal variation of D4 in influents of effluents of WWTPs. However, this study is not summarized here as it was published in Chinese.

Influent and effluent from a WWTP in Shandong Province, China, were collected and analyzed for concentrations of D4 (Qu et al., 2019). However, this study is published in Chinese, thus it is not summarized here.

Wang et al. (2015b) collected grab samples of raw influent and effluent from a municipal WWTP that discharges into the Bohai Sea, Dalian, China. Samples were collected during seven consecutive days, 20 May to 26 May 2014, at 10:00 AM. Mean concentrations of D4 in influent and effluent ranged from 225 to 521 ng/L and from 50 to 181 ng/L, respectively.

Influent, primary clarifier effluent, secondary clarifier effluent, and final effluent were collected from nine WWTPs in Saitama Prefecture, Japan, from July to October, 2013 (Horii et al., 2019). The WWTPs treated mainly domestic wastewater (59-92%) and served 70% of the population in Saitama Prefecture, which is 7,200,000. Samples were collected by grab sampling. Concentrations of D4 in wastewater ranged from <7 to 3,080 ng/L. In addition, composite samples (every 2 h) of influent and effluent were collected on 7 continuous days (25 February to 04 March 2014) via autosamplers at one WWTP. In the composited influent and effluent samples collected for diurnal analysis, mean concentrations of D4 were 560 ng/L and 29 ng/L, respectively.

From a WWTP in Harbin, China, influent and effluent samples were collected at approximately 10:00, 13:00, and 16:00 each day for 3 consecutive weekdays and then uniformly mixed to create one sample (Li et al., 2016). This sampling occurred four times during 2012, in January, April, July, and December. Concentrations of D4 in influent ranged from 16.8 to 103 ng/L (mean value of 62.4 ng/L). In effluent, concentrations of D4 ranged from 10.4 to 59.3 ng/L (mean value of 26.0 ng/L).

Grab samples of effluent were collected from WWTPs located around Tokyo Bay, Japan (Horii et al., 2017). D4 was detected in 100% of the samples collected (N=25). Concentrations of D4 ranged from 4.3 to 200 ng/L, with a mean value of 27 ng/L.

- USA / Canada

From November 2013 to May 2014, samples of sludge were collected from the City of Loveland Wastewater Treatment Plant, Loveland, Colorado and the Drake Wastewater Reclamation Facilities in Fort Collins, Colorado (Zhang, 2014). Concentrations of D4 in sludge samples ranged from 300 to 1,800 ng/g dw.

Sludge samples were collected from a municipal WWTP in Ontario, Canada that serves a population of approximately 285,900 in winter 2011. Mean concentrations of D4 in the sludge samples ranged from 1,290 to 1,770 ng/g dw (Wang et al., 2015a).

- Europe

Sludge was collected from the Bekkelaget Sewage Treatment Plant located in the greater Oslo, Norway area in June 2018 (Ruus et al., 2019). The concentration of D4 in the sludge collected was 57.5 ng/g.

In April 2011, sludge samples were collected from six WWTP in the Catalonia region of Spain (Companioni-Damas et al., 2012b). The mean concentration of D4 in sludge from each WWTP ranged from 2,528 to 15,070 ng/g dw.

Grab samples of dewatered sewage sludge were collected 2 – 8 April, 2012 from a municipal WWTP in Athens, Greece that serves a population of approximately 3,700,000 (Bletsou et al., 2013). Concentrations of D4 ranged from 90 to 130 ng/g dw (N = 7) in sludge samples, with a mean value of 110 ng/g dw.

In 2006, samples of sludge were collected from the Bekkelaget and VEAS Sewage Treatment Plants located in the greater Oslo, Norway area (Schlabach et al., 2007). Concentrations of D4 in the sludge collected from the inlet and outlet ranged from <180 – 1,100 ng/g dw and from 1000 – 2700 ng/g dw, respectively.

Samples of sludge were collected in 2004 and 2005 from 14 WWTPs located in several Nordic countries, including Denmark, Faroe Islands, Finland, Iceland, and Sweden (Kaj et al., 2005a). Concentrations of D4 in these sludge samples ranged from 96 to 960 ng/g dw.

In 2004, sludge samples were collected from 55 WWTPs located throughout (Kaj et al., 2005b). Concentrations of D4 in the collected sludge samples that were above their respective LODs ranged from 130 to 2,300 ng/g dw (N=38).

- Asia

Wang et al. (2015b) collected grab samples of dewatered sewage sludge from a municipal WWTP that discharges into the Bohai Sea, Dalian, China. Samples were collected during seven

consecutive days, 20 May to 26 May 2014, at 10:00 AM. Mean concentrations of D4 in dewatered sludge ranged from 423 to 2260 ng/g dw.

Dewatered sludge was collected from nine WWTPs in Saitama Prefecture, Japan, from July to October, 2013 (Horii et al., 2019). The WWTPs treated mainly domestic wastewater (59-92%) and served 70% of the population in Saitama Prefecture, which is 7,200,000. Samples were collected by grab sampling. The mean concentration of D4 in the dewatered sludge was 360 ng/g ww.

Samples of excess sludge and aerobic sludge were collected from a WWTP in Harbin, China, in January, April, July, and October of 2012 (Li et al., 2016). Concentrations of D4 in the excess sludge and aerobic sludge ranged from 500 to 900 ng/g dw (mean concentration of 700 ng/g dw) and from 400 to 900 ng/g dw (mean concentration of 600 ng/g dw), respectively.

Concentrations of D4 were measured in aqueous and sludge samples from different treatment units of a WWTP in Beijing City, China (Xu et al., 2013). Collected samples were centrifuged to obtain the aqueous (liquid layer) and sludge (solid layer) splits. D4 was detected in all 26 aqueous samples, with concentrations ranging from 50 to 4,300 ng/L. D4 was detected in all 24 sludge samples, with concentrations ranging from 260 to 2,300 ng/g dw.

The occurrence and concentration of D4 was determined in sewage sludge from three different types of WWTPs (domestic, mixed, industrial) in Korea (Lee et al., 2014). Samples were collected from 40 WWTPs during July to October 2011. To obtain a representative sample from each WWTP, the grab dewatered sludge samples were taken in three consecutive days for each sampling campaign and homogenized by shaking. Sludge from domestic WWTPs (N = 16) had a range of concentrations of D4 from <LOQ to 2,910 ng/g dw (mean value of 340 ng/g dw) and was detected in 12.5% of the samples. Sludge from mixed WWTPs (N = 9) had a range of concentrations of D4 from <LOQ to 19,400 ng/g dw (mean value of 2,250 ng/g dw) and was detected in 22.2% of the samples. Sludge from industrial WWTPs (N = 15) had a range of concentrations of D4 from <LOQ to 4,370 ng/g ww (mean value of 330 ng/g dw) and was detected in 13.3% of the collected samples.

From October 2010 to March 2011, a total of 42 dewatered sewage sludge samples were collected from WWTPs in 23 cities, most of which were located in relatively developed provinces of China (Liu et al., 2014). Concentrations of cyclic siloxanes (total of D4, D5, and D6) ranged from <LOQ to 36,000 ng/g (mean value of 1,980 ng/g dw). The average proportions of the total cyclic siloxanes were 45%, 34%, and 21% for D4, D5, and D6, respectively. This distribution of the cyclic siloxanes in inconsistent with other studies, where D5 is usually the predominant compound.

From 2008 to 2013, sludge samples from three oil production WWTP in the Hekou district of China were collected annually. Concentrations of cyclic siloxanes (total of D4, D5, and D6) ranged from $1.67x10^4$ to $2.33x10^5$ ng/g dw (mean value of $8.12x10^4$ ng/g dw; N=18). Relative to the concentrations of D5 and D6, D4 had the lowest concentrations in the sludge samples.

Eight sludge samples were collected from eight WWTPs serving seven large cities located along the Songhua River in China: Harbin (the capital of Heilongjiang Province; population 4.89 million), Jiamusi (population 0.82 million), Mudanjiang (a major city located along the Mudan River, which is a tributary of the Songhua River; population 0.8 million), Qiqihar (population 1.44 million), Changchun (CC; the capital of Jilin Province, population 3.68 million), Jilin (population 2 million), and Songyuan (population 0.52 million), in Heilongjiang and Jilin Provinces, during July 2009 (Zhang et al., 2011). Concentrations of D4 in sediments ranged from 41.8 to 103 ng/g dw. D4 was detected in 100% of the sludge samples collected. The median and mean concentration of D4 in the collected sludge samples was 62.1 ng/g dw and 63.3 (± 17.6) ng/g dw, respectively.

- USA / Canada

Soils were collected from agricultural fields in Ontario, Canada where biosolids from WWTPS had been applied. Samples were collected in 2010, after crop harvest. Concentrations in soil samples ranged from <8.0-17 ng/g dw (Wang et al. 2013).

- Europe

In 2018, soil (0-20 cm) was collected from locations around Oslo, Norway that ranged from forests to urban soils characterized by little plant debris and artificial fertilization (Heimstad et al., 2019). Concentrations of D4 ranged from < LOD to 3.07 ng/g dw.

Beach sand samples were collected from 23 sampling sites along Oporto's coastal area, in the northern part of Portugal (Capela et al., 2019). Sampling was conducted at each site in September 2013 and again in March 2014. Dry sand samples were collected at a depth of 5 cm. Mean concentrations of D4 in these samples ranged from non-detect to 3.35 ng/g dw (detection limit for D4 not reported). These results were generated using a "Quick, Easy, Cheap, Effective, Rugged, and Safe" (QuEChERS) methodology.

Soil samples (0-10 cm) an urban area and a remote area of Portugal as part of a method validation study for the determination of D4 in air (Ramos et al., 2016). Samples from the urban area and the remote area had soil concentrations of D4 of 4.4 ng/g dw and 0.10 ng/g dw, respectively. These techniques were employed for a larger scale study that collected samples from urban areas (N=2), industrial parks (N=2), beach resorts (N=2), and remote areas of Portugal (Ratola et al., 2016). Concentrations of cVMS in soils needles ranged from 5 to 70 ng/g dw, with D4 contributing a mean of 8% to the total concentration. These results were generated using a QuEChERS methodology.

In November 2011, surface soils (0-5 cm) were collected from six urban locations around the city of Barcelona, Spain (Companioni-Damas et al., 2012b). Concentrations of D4 were less than the limit of detection in all soil samples collected (reported detection limit of approximately 0.14 ng/g dw).

Two soil samples from Faroese landfills were collected in December 2014 and analyzed for D4 (Kaj et al., 2005). In both samples, the concentration of D4 was below the LOD (6-10 ng/g dw).

- Asia

Samples of soil were collected at three construction sites, one automobile plant, two paint factories, 20 residential properties and 10 offices located in southwestern China, from January to March, 2017 (Guo et al., 2019b). The greatest concentration of D4 in soil was collected from one of the paint factories (approximately 1,500 ng/g). Concentrations of D4 in soil collected near residential and office properties were comparable to one another, at approximately 5 ng/g.

Soil samples (N=15) were collected in the vicinity of Dongting Lake, the second largest freshwater lake in China, in October 2016 (Zhang et al., 2018). Concentrations of D4 ranged from <LOD to 110 ng/g dw, with mean and median concentrations of 22.2 ng/g dw and 18.8 ng/g dw, respectively.

Soil samples were collected within the boundaries of a WWTP in Harbin, China during July, 2012 (N=11) (Li et al., 2016). Concentrations of D4 in the soil samples ranged from 53.2 to 4,105 ng/g, with mean and median values of 1,404 ng/g and 1,168 ng/g, respectively.

From 2008 to 2013, 52 soil samples from the crude oil-production areas of the Hekou district of China were collected annually (Shi et al., 2015). An additional eight field soil samples were collected from a reference area in the Guangrao district. In soil samples collected from the reference area (N=48), concentrations of D4 ranged from <LOQ to 28.0 ng/g dw (mean value of 3.91 ng/g dw). D4 was detected in 29% of the samples collected from the reference area. In soil samples collected from the oilfields (N=306), concentrations of D4 ranged from <LOQ to 505 ng/g dw (mean value of 43.4 ng/g dw). D4 was detected in 65% of the soil samples collected from the oilfields.

- Antarctica

The surface 1 cm of soil from 11 sites around Antarctica had mean and median D4 concentrations of 14.3 ng/g dw and 13.9 ng/g dw, respectively, and ranged from <MLOQ to 23.9 ng/g dw (Sanchís et al., 2015). Sampling was conducted in January-February 2009 and sites ranged from proximal to Juan Carlos I research station to Deception and Livingston Islands to sites with penguin colonies. It should be noted that the results of this study were questioned by other researchers (Warner et al., 2015; Mackay et al., 2015) due to poor quality control and sample handling, as well as the method of D4 determination.

- USA / Canada

Whole body homogenates of lake trout (*Salvelinus namaycush*; n=70) and walleye (*Sander vitreus*; n=17) collected from the Great Lakes, Kusawa Lake (Yukon), Lake Athabasca (Alberta), and Lake Winnipeg (Manitoba) (McGoldrick et al. 2014a). Mean concentrations were calculated for each species at each sampling location, and ranged from 0.86 to 13 ng/g ww. The levels of D4 were highest in fish collected from the Great Lakes. Lake trout collected in the area of Lake Ontario that is directly influenced by the inflow of the Niagara River consistently had the highest concentrations of D4, ranging from 2.5-28 ng/g ww.

Aquatic biota representing various trophic levels were collected from Lake Erie and analyzed for concentrations of cVMS and evidence of biomagnification. Concentrations of D4 were below detection (<2 ng/g) in composite plankton, 7.0 ng/g ww in burrowing mayfly *Hexagenia*, and ranged from 7.9 to 13 ng/g ww in fish (McGoldrick et al. 2014b).

Concentrations of D4 were also reported in lake trout collected from Laurentian Great Lakes during 2008 – 2012 (McGoldrick et al., 2016). In Lake Superior, concentrations of D4 in lake trout ranged from 1.2-20.4 ng/g ww (7.0±6.8 ng/g ww (mean± st dev); N=15). Lake trout collected from Lake Huron had concentrations of D4 that ranged from 1.2-3.3 ng/g ww (2.3±0.7; N=10). Concentrations of D4 ranged from 1.3-28 in lake trout collected from Lake Ontario (6.7±4.5; N=84). In lake trout and walleye collected from Lake Erie, concentrations of D4 ranged from 2.7-21 (8.2±5.2; N=25).

As part of a long-term monitoring program being conducted in Lake Ontario, an invertebrate and several fish species were collected and mean concentrations of D4 ranged from 0.33-4.60 ng/g ww, 0.10-1.00 ng/g ww, 0.26-1.89 ng/g ww, 0.85-3.93 ng/g ww, 0.21-1.73 ng/g ww, and 6.19-9.57 ng/g ww in mysis, small goby, goby, alewife, rainbow smelt, and lake trout, respectively (Kim 2018a). This sampling was conducted annually from 2011 through 2016, however lake trout was the only species collected in 2015.

In Lake Pepin, Minnesota, mayfly larvae, young-of-year gizzard shad, and sauger were collected annually from 2011 through 2016 (Kim 2018b). Zooplankton were also collected, but were not able to be collected each year of the study. Mean concentrations of D4 ranged from 0.13-1.50 ng/g ww, 0.64-3.38 ng/g ww, 0.86-3.83 ng/g ww, and 0.45-1.28 ng/g ww in zooplankton, mayfly larvae, young-of-year gizzard shad, and sauger, respectively. These concentrations range from being greater than to less than the method detection limit.

Eggs of European starlings (*Sturnus vulgaris*) and a few species of gulls (*Larus argentus, L. glaucescens, and L. californicus*) were collected from a number of sites across Canada with varying land use types (Lu et al., 2017). Starling eggs were collected in April and May of 2013 and 2014. Gull eggs were collected from late April to July in 2011 and 2013. Prior to analysis, eggs were stored and archived in Environment and Climate Change Canada's Wildlife Specimen

Bank. A total of 71 starling and 99 gull egg homogenate samples were analyzed for D4. In starling eggs, concentrations of D4 ranged from less than the method limit of quantification (MLOQ; 0.94 ng/g ww) to 26.4 ng/g ww, with a detection frequency of 55%. Concentrations of D4 in starling eggs were found to be related to the land-use of the sampling sites, with the greatest concentrations being found at sites proximal to landfills and the lowest concentration being found at rural sites. In gull eggs, concentrations of D4 ranged from <MLOQ to 31.4 ng/g ww, with a detection frequency of 86%.

Another monitoring study conducted in Canada measured concentrations of D4 in the blood plasma of common snapping turtles (*Chelydra s. serpentine*), double-crested cormorants (*Phalacrocorax auritus*), and Northwest Atlantic harbor seals (*Phoca vitulina concolor*) (Wang et al., 2017). Mean concentrations of D4 in the blood of turtles sampled from Hamilton Harbor, Ontario and Toronto Harbor, Ontario (considered by the study as contaminated sites) were 0.122 and 0.091 ng/g ww, respectively, compared to 0.077 ng/g ww at a reference site. Mean concentrations in the blood of cormorants from Toronto Harbor and Hamilton Harbor were 0.051 and 0.085 ng/g ww, respectively, no different from 0.083 ng/g ww at a reference site. Mean concentrations in the blood of the harbour seals were 0.314 ng/g ww in the St. Lawrence Estuary (considered by the study as a contaminated site) compared to 0.186 ng/g at a reference site in the northern Gulf of St. Lawrence. These results were generated using a QuEChERS methodology.

In 2007, biota were collected from Lake Opeongo, Ontario and were analyzed for cVMS (Powell 2010). Mean concentrations of D4 ranged from 0.87 to 3.77 ng/g ww in fish tissues and 0.43 ng/g ww in zooplankton; however, cVMS contamination was found in all reagent blanks, and the data, therefore, are not considered reliable.

- Europe

In the autumn of 2018, the Norwegian Institute for Water Research (NIVA) conducted monitoring of biota within the Inner Oslofjord (Ruus 2019). Collected aquatic biota species included polychaetes (N=3), krill (*Euphausiacea*; N=3), prawn (*Pandalus borealis*; N=3), blue mussels (*Mytilus edulis*; N=3), Atlantic herring (*Clupea harengus*; N=3), and Atlantic cod (*Gadus morhua*; N=15). In cod liver, D4 was detected in 100% of the samples, with concentrations ranging from 16.2 to 130 ng/g ww (mean concentration of 65.8 ng/g ww). Concentrations of D4 were non-detectable in the other aquatic biota species collected. Additionally, herring gull (*Larus argentatus*) blood and egg samples were collected in spring 2018. In herring gull blood, concentrations of D4 were < 3.8 ng/g ww (N=15). In herring gull eggs, D4 was detected in 12/15 egg, and concentrations of D4 ranged from < 1.0 to 6.45 ng/g ww (mean concentration of 1.36 ng/g ww).

Zooplankton, mysis (*Mysis relicta*), vendace (*Coregonus albula*), European smelt (*Osmerus eperlanus*), and brown trout (*Salmo trutta*) were collected from Lake Mjøsa, a large lake in Norway, in 2018 (Jartun 2019). In zooplankton, D4 was detected in 100% of the samples (N=3), and concentrations of D4 ranged from 1.2 to 1.5 ng/g ww (mean concentration of 1.3 ng/g ww). In mysis, D4 was detected in 66% of the samples (N=3), and concentrations of D4 ranged from <LOQ to 1.4 ng/g ww (mean concentration of 0.93 ng/g ww). In vendace, D4 was detected in

80% of the samples (N=10), and concentrations of D4 ranged from <LOQ to 2.1 ng/g ww (mean concentration of 1.2 ng/g ww). Concentrations of D4 were below the LOQ in all smelt and brown trout collected from Lake Mjøsa. Brown trout were also collected from Lake Femunden, with a catchment area that consists of bare mountains and forests within a national park; the concentration of D4 was below the LOQ in all brown trout (N=10) collected from Lake Femunden.

Several terrestrial wildlife species were collected from around Oslo, Norway in 2018 (Heimstad et al., 2019). Collected species included depurated earthworms (*Lubricidae*; N=5), fieldfare (*Turdis pilaris*) eggs (N=10), sparrowhawk (*Accipiter nisus*) eggs (N=9), brown rats (*Rattus norvegicus*) liver (N=9), red fox (*Vulpes vulpes*) liver (N=10), and badger (*Melis melis*) liver (N=10). Earthworms were collected at the same locations as the aforementioned soil samples. D4 was not detected in earthworms, fieldfare eggs, sparrowhawk eggs, or badger liver. In brown rat liver, concentrations of D4 ranged from <LOD to 6.80 ng/g ww, with a mean concentration of 1.48 ng/g ww. In red fox liver, concentrations of D4 ranged from <LOD to 13.3 ng/g ww, with a mean concentration of 2.45 ng/g ww.

Livers of Atlantic cod collected in 2017 at research stations in Norway were analyzed for concentrations of D4 (Green et al., 2018). Cod were collected from Inner Oslofjord, Bergen Harbour, Tromsø Harbour, and Isfjorden, Svalbard. Concentrations of D4 in liver of cod collected from Inner Oslofjord ranged from <LOQ to 79.6 ng/g ww, with a median concentration of 40.2 ng/g ww. Concentrations of D4 in liver of cod collected from Bergen Harbour ranged from <LOQ to 571 ng/g ww, with a median concentration of 36.4 ng/g ww. Concentrations of D4 in liver of cod collected from Tromsø Harbour ranged from <LOQ to 59.7 ng/g ww, with a median concentration of 18.5 ng/g ww. Of the 12 cod livers collected from Isfjorden, only one had a concentration of D4 above the LOQ, at 27.4 ng/g ww.

In 2017, bream (*Abramis brama*) were collected from riverine sites around Germany (Radermacher et al., 2020). For comparison, bream from Lake Belau and eelpout (*Zoarces viviparus*) from coastal areas (Baltic and North Seas) from were also collected. Bream collected from the Gündingen site of the Saar River, Bimmen site on the Rhine River, and Jochenstein site on the Danube river had concentrations of D4 of 90.7 ng/g ww, 92.3-93.3 ng/g ww (N=2), and 50.4 ng/g ww, respectively. Bream from the other 13 river sites had concentration of D4 below the LOQ, as the bream from Lake Belau and the eelpout from the Baltic and North Seas. This study also analyzed specimens from the German Environmental Specimen Bank. Analysis of the archived samples found the greatest concentration of D4 in fish from the Rhine River in 2011 (216 ng/g ww) and the Saar River in 2009 (321 ng/g ww).

As part of a long-term monitoring program being conducted in Inner Oslofjord, Norway, an invertebrate and two fish species were collected annually from 2011 through 2016 (Kim 2018c). Mean concentrations of D4 ranged from 0.31-1.63 ng/g ww, 4.47-11.1 ng/g ww, and 0.67-3.36 ng/g ww in northern shrimp (*Pandalus borealis*), Atlantic herring, and Atlantic cod, respectively.

Different species of algae and seaweed were collected from several sites in the Atlantic (North and centre regions of Portugal), and the Mediterranean (coast of the Region of Murcia in

southeast Spain and surroundings of Marseille city in the south of France) in 2016 (Rocha et al., 2019). Concentrations of D4 ranged between <0.04 to 5.00 ng/g dw. These results were generated using a QuEChERS analytical methodology.

Sanchís et al. (2016) also collected 16 samples of different autochthonous species of fish (trout, gobio, black bass, bleak, eel, barbell, pike, and perch) from the Xúquer River, in the Catalonia region of Spain. Sampling was done at five locations of varying proximity to potential point sources. D4 was detected in 93.8% of the samples, with concentrations of D4 ranging from <MLOD to 9.40 ng/g ww (mean value of 1.68 ng/g ww). This study also measured D4 in fish purchased at local supermarkets. In purchased fish samples, D4 was detected in 100% of the samples, with concentrations of D4 ranging from 1.41 to 29.0 ng/g ww (mean value of 9.33 ng/g ww).

Eggs of three seabird species, common eider (*Somateria mollisima*), European shag (*Phalacrocorax aristotelis aristotelis*), and European herring gull (*Larus argentatus*), were collected from two remote Norwegian islands during the breeding season between May and June 2012 (Huber et al., 2015). Six pooled samples per species were analyzed. D4 was not detected in any of the bird eggs collected (LOD=2.1 ng/g ww).

Samples of Atlantic cod livers were collected in November 2010 and April 2011 near Tromsø, Norway (Warner et al., 2014). During each sampling campaign, cod were collected from a harbor near Tromsø and from a more remote location. In cod livers collected from near Tromsø, concentrations of D4 ranged from 15.7 to 111 ng/g lw (N=12), with median and mean concentrations of 47.5 ng/g lw and 58.8 ± 24.7 ng/g lw, respectively. Concentrations of D4 ranged from 5.6 to 15.0 ng/g lw (N=8), with median and mean concentrations of 10.8 ng/g lw and 10.3 ± 3.3 ng/g lw, respectively, in cod livers collected from the more remote location.

In July 2009, representative species of the marine ecosystem were collected from Adventfjorden, Kongsfjorden, and Liefdefjorden on the Norwegian archipelago of Svalbard (Warner et al., 2010). Samples consisted of mixed zooplankton (predominantly calanoid copepods, krill, and pelagic amphipods), Atlantic cod and shorthorn sculpin (*Myxocephalus scorpius*) livers, and bearded seal (*Erignathus barbatus*) blubber. Concentrations of D4 were below the MDL in all samples collected. MDLs ranged from 2.2 to 10.1 ng/g ww.

Common ragworm (*Hediste diversicolor*) and flounder (*Pleuronectes flesus*) were collected from six locations within the Humber Estuary, off the east coast of England, in September and October 2009 (Kierkegaard et al., 2011). Concentrations of D4 were below the LOQ in 11 of the 19 ragworm samples and in 25 of the 34 flounder samples. The range of concentrations of D4 in ragworm samples was from <LOQ to 20 ng/g ww and was from < LOQ to 10.4 ng/g ww in the flounder fillets.

A study conducted in the Norwegian Arctic in 2008 (Evenset et al., 2009) analyzed five Atlantic cod liver samples, six polar cod liver samples, and five polar cod whole-body homogenates for D4. Concentrations of D4 were found to range from 2.9 to 3.9 ng/g ww in Atlantic cod livers, <LOD to 9.2 ng/g ww in polar cod livers, and 3.6 to 7.8 ng/g ww in whole-body homogenates of

polar cod. The same study also analyzed liver samples from nine kittiwake (*Rissa tridactyla*) and five common eider (*Somateria mollissima*); D4 was detected in 4 of the analyzed kittiwake livers with concentrations ranging between 2.6 and 3.5 ng/g ww. D4 was not detected in the livers of the common eider.

Concentrations of D4 were measured in Atlantic herring and grey seals (*Halichoerus grypus*) from the Baltic Sea (Kierkegaard et al., 2013). Herring were collected in 2007 and seals were collected in 2008, along with a few more herring samples collected nearby. Concentrations of D4 were measured in herring fillet and seal blubber. The mean (± st dev) concentration of D4 in herring fillet was 12 ± 10 ng/g lw. In seal blubber, concentrations of D4 were less than the LOQ, indicating that D4 was not biomagnifying in the seals.

In 2006, aquatic biota were collected from the Inner and Outer Oslofjord, Norway (Schlabach et al., 2007). Matrices collected and analyzed included blue mussel, flounder liver, flounder fillet, cod liver, and cod stomach contents. In blue mussel, concentrations of D4 ranged from 1.3 – 2.3 ng/g ww (N=3). In the one flounder liver and one flounder fillet, the concentration of D4 was 2.6 ng/g ww and 1.9 ng/g ww, respectively. Concentrations of D4 in the cod stomach contents (N=3) and cod liver (N=3) ranged from 5.0 – 9.3 ng/g ww and from 81.2 – 134.4 ng/g ww. One additional cod liver that was collected at the same sampling location in 2004 had a concentration of D4 of 70.0 ng/g ww.

Forty-five samples of fish, marine mammals, and seabird eggs were collected from various Nordic locations in 2004 and 2005, and analyzed for concentrations of D4 (Kaj et al., 2005a). Specifically, the study examined pooled liver samples from 9 species of marine and freshwater fish (eelpout, flounder, cod, sculpin, dab, Arctic char, brown trout, pike and vendace), as well as pooled blubber samples from 4 types of marine mammal (seal, pilot whale, whiteside dolphin, and common porpoise) and eggs from 3 species of seabirds (fulmar, black guillemot and herring gull). In the liver of marine and freshwater fishes, concentrations of D4 ranged from < 5.0 to 70 ng/g ww (detected in 5 of 11 samples) and from <5.0 to 8.9 ng/g ww (detected in 3 of 10 samples), respectively. The concentration of D4 was greater the LOD in only one of 7 samples of marine mammal blubber, at a concentration of 12 ng/g ww. In seabird eggs, the concentration of D4 was below the MDL (5 ng/g ww) in all 17 samples collected.

In 2004, fish samples were collected from sites in Sweden ranging from background areas to those with potential point sources of emission (Kaj et al., 2005b). Concentrations of D4 in the collected fish fillet samples were all below the LOD (5 ng/g ww; N=19). Limited information was reported regarding the species of fish collected.

- Asia

As part of a long-term monitoring program being conducted in Tokyo Bay, Japan, several fish species were collected annually from 2011 through 2016 (Kim 2018d). Mean concentrations of D4 ranged from 6.18-28.6 ng/g ww, 8.20-25.6 ng/g ww, 5.71-11.4 ng/g ww, 35.7-72.8 ng/g ww, and 13.6-32.6 ng/g ww in Japanese anchovy, Japanese scaled sardine, white croaker, Japanese sea bass, and red barracuda, respectively.

In September 2015, a total of 205 mollusks, including mussel (*Mytilus galloprovincialis*), venus clam (*Cyclina sinensis*), and oyster (*Crassotrea talienwhanensis*) were collected from culturing rafts near seven coastal cities in the Bohai Sea, China (Zhi et al., 2019). Concentrations of D4 in the mollusks ranged from <3.5 to 47.6 ng/g ww, and was detected in 71% of the mollusks collected. The mean (± st dev) concentration of D4 in mollusks was 15.7 ± 12.3 ng/g ww.

Fish were collected (N=85; 9 species) from the Ara, Tama, and Yoro rivers, which all flow into Tokyo Bay, Japan (Horii, et al., 2013). Sampling was conducted between October and November, 2012. Fish were analyzed as whole-body homogenates and the mean concentration of D4 found in fish tissue was 35 ng/g ww.

Six fish species were collected from Yugawara Harbor, in Kanagawa Prefecture, Japan, in 2012-2013 (ECC 2019). Species collected included the Kidako moray (*Gymnothorax kidako*), spotted tail morwong (*Cheilodactylus zonatus*), largescale blackfish (*Girella punctata*), banded houndshark (*Triakis scyllium*), grass puffer (*Takifugu niphobles*), and smallspotted dart (*Trachinotus baillonii*). Concentrations of D4 in the collected fish ranged from 1.9 to 7.1 ng/g ww.

- Antarctica

Phytoplankton and krill were collected from the Southern Ocean in February 2009 (Sanchís et al., 2015). Mean and median concentrations of D4 in phytoplankton were 0.93 ng/g dw and 0.70 ng/g dw, respectively, and ranged from 0.30 to 3.50 ng/g dw (N=11). In krill (N=11), mean and median concentrations of D4 were 48.9 ng/g dw and 41.1 ng/g dw, respectively, and ranged from 12.3 to 117 ng/g dw. Samples of vegetation (lichens, grasses, mosses) were collected in January-February 2009. Sites ranged from proximal to Juan Carlos I research station, to the areas of Deception and Livingston Islands, to sites with penguin colonies. Mean and median concentrations of D4 in vegetation samples were 6.16 ng/g dw and 5.38 ng/g dw, respectively, and ranged from <MLOQ to 21.0 ng/g dw (N = 17). It should be noted that the results of this study were questioned by other researchers (Warner et al., 2015; Mackay et al., 2015) due to poor quality control and sample handling, as well as the method of D4 determination.

- Europe

In the winter of 2013 and 2014, blood samples were randomly collected from healthy blood donors living in Munich, Germany, and the surrounding areas (Fromme et al., 2015). Blood samples were collected from a total of 42 subjects, 21 males and 21 females. D4 was detected in 31% of the samples, with concentrations of D4 ranging from <0.18 to 0.73 µg/L.

The concentration of D4 in exhaled air was quantified, as it reflects blood concentration and therefore internal exposure to D4 (Biesterbos et al., 2014). Exhaled air was collected from 15 consumers who regularly used personal care products, and exhaled air was collected again from the same individuals following 24 h of no personal care product usage. The mean concentration of D4 in exhaled air ranged from 2 to 45 ng/L. After 24 h of no personal care product use, the mean concentration of D4 in exhaled air was below 4 ng/L.

A study was conducted in Norway to quantify the concentrations of D4 in blood plasma of pregnant and post-menopausal women (Hanssen et al., 2013). A total of 94 plasma samples were analyzed from the post-menopausal cohort. From the post-menopausal cohort, greater than 85% of the women had concentrations of D4 above the LOQ (2.74 ng/mL), with a maximum concentration of 12.7 µg/L. A total of 17 plasma samples were analyzed from the pregnant cohort. In the pregnant cohort, only 18% of the blood plasma samples had concentrations of D4 greater than the LOQ (1.48 µg/L) with a maximum blood plasma concentration of D4 of 2.69 µg/L.

In 2004, samples of breast milk were collected from women in Sweden (Kaj et al., 2005b). A total of 39 samples of breast milk were collected and analyzed for D4. Of those 39 samples, three samples had a concentration of D4 above the LOD (2 µg/L); 2.9, 3.5, and 10 µg/L.

- Asia

Between January and March 2017, blood plasma was collected from 170 industrial facility workers and 100 individuals from the general population in residential areas in southwestern China (Guo et al., 2019b). Concentrations of D4 in blood plasma from the industrial facility workers ranged from 3.9 to 84 ng/mL (detection frequency = 100%). In blood plasma from the general population, concentrations of D4 ranged from 2.1 to 7.8 ng/mL (detection frequency = 13%).

Blood plasma and abdominal fat were collected to determine the concentration of D4 in industry workers in China (Xu et al., 2015). In total, 1047 participants were enrolled in the study; the occupational group contained 528 participants from seven different industrial facilities (2 construction sites, 2 paint production plants, 1 automobile plants, 1 engine plant, and 1 textile plant), and the control group contained 519 participants that did not have an industrial occupation. Median concentrations of D4 in blood plasma from the seven industrial facilities

ranged from 3.53 to 25.5 µg/L, with individual sample concentrations ranging from <LOQ to 75.1 µg/L (detection frequency ranged from 15% to 67%). Abdominal fat samples collected from occupational group (N=41) contained concentrations of D4 that ranged from 86.8 to 306 ng/g (median concentration 177 ng/g; 100% detection frequency). In the control group, D4 was only detected in 3.7% of the plasma samples, with concentrations ranging from <LOQ to 5.95 µg/L, and a median concentration of 2.50 µg/L. Abdominal fat samples collected from male (N=70) and female (N=179) participants in the control group contained concentrations of D4 that ranged from 5.95 to 65.6 ng/g (median concentration of 15.0 ng/g; 17% detection frequency) and from 4.00 to 141 ng/g (median concentration of 46.7 ng/g; 46% detection frequency), respectively. (Note: median concentration reflects the median value of concentrations exceeding the LOQ).

In 2011, blood plasma was collected from cohorts of people that either currently worked in a siloxane production facility (N=72), lived downwind of a siloxane production facility (N=14), or were a reference group that represented background exposure (N=58) (Xu et al., 2012). Mean concentrations of D4 in the blood plasma of current workers and those that lived downwind of a siloxane production facility were 206 ng/g and 13.5 ng/g, respectively. In blood plasma collected from the reference group, D4 was detected in only two samples (1.2 and 3.6 ng/g). Blood plasma samples were also collected from 32 former siloxane industry workers, and 25 of those workers provided an additional sample approximately 6 weeks later. Generally, the plasma concentrations of both cyclic and linear methyl siloxanes decreased with the increase of days since the worker had left the facility. Notably, none of the methyl siloxanes were detectable in plasma samples of former workers who had left the facility for more than 85 days.

A total of 56 food contact silicone rubber products were purchased from retail stores in China in 2017-2018 (Feng et al., 2018). Product categories included bottle nipples (N=28) and bakeware, which included moulds (N=11), pastry bags (N=6), chopping boards (N=6), ice lattices (N=2), biscuit mould (N=1), macaron pad (N=1), and funnel (N=1). Concentrations of D4 in bottle nipples ranged from <MDL to 16.7 µg/g, with a median and mean concentration of D4 in bottle nipples of 2.26 µg/g and 3.40 µg/g, respectively. Concentrations of D4 in bakeware ranged from <MDL to 440 µg/g, with a median and mean concentration of D4 in bakeware of 6.40 µg/g and 42.9 µg/g, respectively. The greatest concentration of D4 was found in the macaron pad.

Results of study which analyzed silicone bakeware for volatile compounds were published by Li et al. (2018), but the study could not be summarized here as it is published in Chinese.

In 2017, a total of 30 hair care products, including shampoo (N=9), hair gel (N=13), and hair mousse (N=8), were purchase from retail stores in Hanoi, Vietnam, and were acquired directly from hair salons (Tran et al., 2018). Concentrations of D4 in these products ranged from 1.56 to 70.5 µg/g. The greatest concentration of D4 was found in a hair gel. The median and mean concentration of D4 in all the products tested were 14.1 µg/g and 18.0 µg/g, respectively.

From January to March 2017, 32 paint samples were collected in China, comprising 13 paint product samples from three construction sites, 15 paint product samples from two paint factories, and 4 car paint samples from a single automobile factory (Guo et al., 2019b). Concentrations of D4 ranged from 7.1 to 31 ng/g, from 218 to 380 ng/g, and from 11 to 52 ng/g in paint product samples collected from construction sites, a car factory, and paint factories, respectively.

A total of 123 personal care products were purchased from retail stores in Oporto, Portugal in 2014 (Capela et al., 2016). Product categories included moisturizers (N=23), toothpastes (N=12), toilet soaps (N=15), body and hair washes (N=50), deodorants/antiperspirants (N=12), and shaving products (N=11). Concentrations of D4 in these products ranged from non-detect to 267.0 µg/g. The greatest concentration of D4 was found in hair shampoo. D4 was detected in 85% of the products tested. The median and mean concentration of D4 in all the products tested were 2.43 µg/g and 25.11 µg/g, respectively. These results were generated using a QuEChERS analytical methodology.

In 2011, 51 cosmetic and personal care products were purchased from retail stores in Utrecht, the Netherlands (Dudzina et al., 2014). Product categories included hair care products (N=10), deodorants/antiperspirants (N=11), skin lotions (N=16), sun care products (N=8), cosmetics (N=5), and toothpaste (N=1). Concentrations of D4 in these products ranged from non-detect to 5,000 µg/g. The greatest concentration of D4 was found in a deodorant/antiperspirant cream. The median and mean concentration of D4 in all the products tested were 11 µg/g and 180 µg/g, respectively.

Between January to March 2012, 33 samples of industrial products and additives were collected and analyzed (Xu et al., 2015). Product types included home paint products (N=24), car shell paint products (N=3), car shell polish (N=1), machine lubricant (N=2), fabric softening agents (N=2), and a spot remover (N=1). The greatest concentration of D4 was found in the spot remover, at 1,450 µg/g. Concentrations of D4 in the home paint products, car shell paint products, car shell polish, machine lubricant, and fabric softening agents ranged from <LOQ to 89 µg/g, from 99 to 134 µg/g, 212 µg/g, from 338 to 450 µg/g, and from 663 to 789 µg/g, respectively.

A total of 158 personal care products were purchased in 2009 from retail stores in Shanghai, China; all of the products were manufactured in China (Lu et al., 2011). Product categories included toothpastes, hair care products, body washes, toilet soaps, skin lotions, and makeup. Concentrations of D4 in these products ranged widely, from <0.02 to 72.9 µg/g. The greatest concentration of D4 was found in hair shampoo. D4 was detected in 59% of the products tested. The median and mean concentration of D4 in all the products tested were 0.29 µg/g and 5.24 µg/g, respectively.

In 2008, 18 hair care products were purchased for chemical analysis (Helm et al., 2018). Product categories included hot oil treatments, anti-frizz/polish, leave-in conditioner, root stimulator, hair lotion, and relaxer. Concentrations of D4 in these products ranged widely, from non-detect to 2,590 µg/g. The greatest concentration of D4 was found in an anti-frizz/polish product. D4 was detected in 61% of the products tested. The median concentration of D4 in all the products tested was 13 µg/g.

Concentrations of D4 were determined in 252 cosmetics and personal care products purchased from retail stores in Canada from December 2007 to February 2008 (Wang et al., 2009). Product categories included fragrances, hair care products, deodorants/antiperspirants, nail polishes, lotions, skin cleansers, and baby products. Concentrations of D4 in these products ranged widely, from <8 to 11,000 µg/g. The greatest concentration of D4 was found in a body lotion. D4 was detected in only 4.8% of the products tested.

In 2006, 76 personal care and household products were purchased in Albany, New York and in Tsukuba, Japan (Horii and Kannan, 2008). Product categories included cosmetics (N=6), hair-care products (N=13), body washes (N=9), skin lotions (N=18), nursing nipples (N=4), cookware (N=13), sealants (N=3), household cleaning products (N=6), and other (N=4). Concentrations of D4 in these products ranged widely, from <0.35 to 9,380 µg/g. The greatest concentration of D4 was found in furniture polish. D4 was detected in 51% of the products tested. The median and mean concentration of D4 in all the products tested were 0.62 µg/g and 141 µg/g, respectively.

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