DIMETHICONE

(CAS #63148-62-9/9006-65-9/9016-00-6)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: August 28, 2023

Expiration Date: August 28, 2028

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING
1367 Connecticut Ave., N.W., Suite 300
Washington, D.C. 20036

GreenScreen® Polymer Substance Assessment

Polymer Substance Name: Dimethicone (CAS #63148-62-9/9006-65-9/9016-00-6)

Trade Name: Unspecified

Manufacturer: Unspecified

Method Version: GreenScreen® for Safer Chemicals v1.4

Assessment Details[1]:

Assessment Type:	Certified
Initial GreenScreen® Assessment	
Assessment (v1.4) Prepared By:	Jennifer Rutkiewicz, Ph.D. Senior Toxicologist ToxServices LLC
Quality Control Performed By:	Bingxuan Wang, Ph.D., D.A.B.T. Senior Toxicologist ToxServices LLC
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Updated GreenScreen® Assessment	
Assessment (v1.4) Updated By:	Rachel Doerer, M.P.H. Toxicologist, ToxServices LLC
Quality Control Performed By:	Bingxuan Wang, Ph.D., D.A.B.T. Senior Toxicologist ToxServices LLC
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[1] **Assessment Type**: GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen Profiler or equivalent);-**Assessment Prepared By**: Licensed GreenScreen® Profilers must provide name of organization; Authorized GreenScreen® Practitioners must provide their name;

Assessment Prepared For: Optional for Licensed GreenScreen® Profilers, mandatory for Authorized Practitioners; **Date Assessment Completed**: Assessments by Licensed GreenScreen® Profilers require quality control tracked via internal documentation;

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GREENSCREEN BENCHMARK™ SUMMARY FOR DIMETHICONE (CAS #63148-62-9/9006-65-9/9016-00-6)

Dimethicone is a liquid silicone polymer that is white and almost odorless. Its viscosity may range from 20 cSt to 60,000 cSt (100-350 cSt are generally used for cosmetics). According to the Cosmetic Ingredient Review (CIR), dimethicone is a mixture of fully methylated linear siloxane polymers end blocked with trimethylsiloxy units, and the International Nomenclature Cosmetic Ingredient (INCI) name dimethicone corresponds to polymers with the CAS #s 9006-65-9, 9016-00-6, and 63148-62-9. Dimethicone has both cosmetic and therapeutic uses, including use in topical creams and ointments to distribute active ingredients, as an antifoaming agent, as a skin and hair conditioning agent, as a lice treatment, and as an antiflatulent and antibloating agent. This GreenScreen® assessment applies specifically to high molecular weight dimethicone.

Dimethicone was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes"). This is based on the following hazard score combinations:

- Benchmark 2c
  - Very High Persistence-P + Moderate Group II Human Toxicity (eye irritation-IrE)

Data gaps (DG) exist for endocrine activity-E and repeated dose neurotoxicity-Nr*. As outlined in Annex 5 (GreenScreen Benchmark™ Data Requirement), dimethicone meets the requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if dimethicone were assigned a High score for the data gap E or Nr*, it would be categorized as a Benchmark 1 Chemical.

The GreenScreen® for dimethicone has been updated over time. ToxServices' original GreenScreen® assessment was performed in 2019 under version 1.4 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. ToxServices maintained this chemical's BM-2 score with this version 1.4 update.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for respiratory sensitization; use of *in vitro* data for mutagenicity and endocrine activity; and reliance on physicochemical properties to assess bioaccumulation. The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties:

- Type I: Uncertainties related to the input data used
- Type II: Uncertainties related to extrapolations made

Type I (input data) uncertainties in dimethicone's NAMs dataset include lack of sufficient *in vivo* data for all critical endocrine pathways, lack experimental data and no validated test methods for respiratory sensitization, and no experimental data for bioaccumulation. Dimethicone's Type II (extrapolation output) uncertainties include reliance on structural alerts for the respiratory sensitization endpoint where the applicability domain is not defined; uncertain relevance of *in vitro* endocrine data for the qualifying constituents; reliance on *in vitro* data for genotoxicity and endocrine activity that captures key events but may not account for all events in an adverse outcome pathway and/or may not account for *in vivo* metabolism, lack of consideration of non-immunologic mechanisms for respiratory sensitization during the assessment of structural alerts, and uncertainty in the bioaccumulation of oligomers when evaluation is solely based on physicochemical properties of the polymers. Some of dimethicone's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 1. GreenScreen® Polymer Hazard Summary Table[2,3,4]

GreenScreen® Polymer Hazard Summary Table for Dimethicone																							
		Group I Human					Group II and II* Human									Ecotox		Fate		Physical		
	% By Weight	Carcinogenicity	Genotoxicity/Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability	GreenScreen Benchmark™
								single	repeat*	single	repeat*	*	*									
Polymer Substance	98.5 – 101.1	**L**	**L**	*L*	**L**	DG	**L**	**L**	**L**	*L*	DG	**L**	*L*	**L**	*M*	**L**	*L*	*vH*	*vL*	*L*	**L**	2

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that Group II Human Health endpoints have four hazard scores (i.e., vH, H, M and L) instead of three (i.e., H, M and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints.

[2] See Appendix A for a glossary of hazard endpoint acronyms.
[3] See Appendix B for alternative GreenScreen® Hazard Summary Table (Classification presented by exposure route).
[4] For Systemic Toxicity and Neurotoxicity, repeated exposure data are preferred. Lack of single exposure data is not a Data Gap when repeated exposure data are available. In that case, lack of single exposure data may be represented as a shaded cell instead of DG.

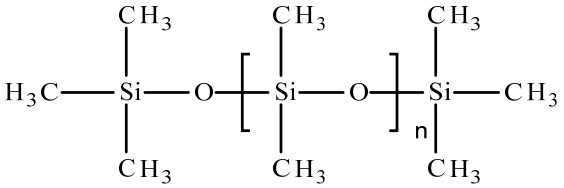
POLYMER PROPERTIES AND CONSTITUENTS

Dimethicone is a liquid silicone polymer that is white and almost odorless. Its viscosity may range from 20 cSt to 60,000 cSt (100-350 cSt are generally used for cosmetics) (CIR 2003). According to the Cosmetic Ingredient Review (CIR), dimethicone is a mixture of fully methylated linear siloxane polymers end blocked with trimethylsiloxy units, and the International Nomenclature Cosmetic Ingredient (INCI) name of dimethicone corresponds to polymers with the CAS #s 9006-65-9, 9016-00-6, and 63148-62-9 (CIR 2003). Dimethicone has both cosmetic and therapeutic uses, including use in topical creams and ointments to distribute active ingredients, as an antifoaming agent, as a skin and hair conditioning agent, as a lice treatment, and as an antiflatulent and antibloating agent (HSDB 2017).

Dimethicone is produced first by a reaction between methyl chloride (generated from a reaction between methanol and hydrochloric acid) and silicone to produce dimethyldichlorosilane, which is the starting monomer. According to at least one report, this reaction may involve a copper catalyst, but the specific identity and concentration in the finished polymer were not reported (ECETOC 2011), and CIR (2003) does not identify any catalysts as typical impurities in cosmetic grade dimethicone. Dimethyldichlorosilane forms dimethyldisilanol in the presence of water; dimethyldisilanol is unstable and readily condenses to produce linear and cyclic oligomers. The cyclic oligomers are generally used to produce high purity dimethicone by opening the ring with a base catalyst, which is later neutralized, followed by further polymerization (ECETOC 2011, O'Lenick 1999).

This GreenScreen® assessment applies specifically to high molecular weight dimethicone.

Table 2. Structural Properties for the Polymer Substance

Property	Description	Reference
Molecular Formula	$(CH_3)_3SiO\text{-}(Si(CH_3)_2O)_x\text{-}Si(CH_3)_3$	CIR 2022
General polymer class	Siloxanes and silicones	CIR 2003, 2022
Structure (include whether monomers are blocked and the pattern)		CIR 2022
Number average molecular weight (Mn)	50,000 (typical)	Sigma Aldrich 2023
Weighted-average molecular weight (Mw)	95,000 (typical)	Sigma Aldrich 2023
Physical state	Liquid	CIR 2003, 2022
Percent Amine Nitrogen (%A-N) [5]	Not Applicable	
Reactive Functional Group (with their respective charge), and	Not Applicable	
	Not Applicable	

[5] The percent of amine nitrogen (or other cationic atom) can be used in the cationic nitrogen polymer Structural Activity Relationships (SARs) for estimation of aquatic toxicity.

Property	Description	Reference
Functional Group Equivalent Weight		
Overall Charge	No charge	Expert judgement
Solubility (mg/L water @ 25ºC)	Virtually insoluble < 1 ng/L (predicted)	ECETOC 2011
Swellability (Insoluble/non-water absorbing ("non-swellable"), or Water absorbing ("swellable"))	Insoluble/non-water absorbing	ECETOC 2011
Particle Size Distribution (microns)	Not Applicable	
Other key characteristics (e.g., surface chemistry)	N/A	

Table 3. Inventory of Polymer Substance Constituents

Constituent	Chemical Name	CASRN	Weight Percent (Wt %) in Polymer Substance	Additional Information (synonyms, etc.)
1) Polymer Substance:				
a) Polymer species > 0 ppm (0%)	Dimethicone	63148-62-9/9006-65-9/9016-00-6/	98.5-101.1%	Typical values for cosmetic-grade (CIR 2003, 2022)
b) Residual Monomer(s) ≥ 100 ppm (0.01%)	None identified	N/A	N/A	The starting monomer dimethyl-dichlorosilane is extremely reactive and will self-react to form circular and linear siloxanes (there is no residual monomer) (OECD 2010)
c) Oligomer(s) with a molecular weight (MW) below 500 Dalton	Octamethyl-cyclotetrasiloxane	556-67-2	<1%	Typical values for cosmetic grade (CIR 2003)
	Decamethylcyclo-pentasiloxane	541-02-6	<1%	
d) Oligomer(s) with a molecular weight (MW) below 1000 Dalton	None identified	N/A	N/A	N.A
e) Stabilizer(s) ≥ 100 ppm 0.01%)	None identified	N/A	N/A	N.A
f) Substance Impurities ≥ 100 ppm (0.01%):				
i) Catalyst	None identified	N/A	N/A	Specific identities and

Constituent	Chemical Name	CASRN	Weight Percent (Wt %) in Polymer Substance	Additional Information (synonyms, etc.)
				levels of catalysts not identified; CIR does not report catalysts as typical impurities in cosmetic grade (CIR 2003)
ii) Other	None identified	N/A	N/A	CIR does not report additional impurities in cosmetic grade (CIR 2003)

Qualifying constituents present at >0.1% in the polymer include octamethylcyclotetrasiloxane (CAS #556-67-2 and decamethylcyclopentasiloxane (CAS #541-02-6), which are present at <1% each (CIR 2003). Qualifying constituents are evaluated under endpoints for which no data are available for the polymer substance, a surrogate, or a similar polymer substance.

SIMILAR POLYMER SUBSTANCES
Note: The term "similar polymer substance" in the GreenScreen® guidance v1.4 is used for applying GHS bridging principles. "Similar polymer substance" is defined as a polymer similar to the original polymer but with residual or unreacted monomers and other impurities equal to or greater than the concentration of the same monomer or impurity in the original polymer (CPA 2018b).

No similar polymer substances (i.e., polymers with the same monomer identities) to dimethicone assessed in this screen were identified.

CHEMICAL SURROGATES:
Dimethicone has a relatively complete dataset; therefore, no surrogates were identified for this evaluation.

ENVIRONMENTAL TRANSFORMATION PRODUCTS
Identify feasible and relevant environmental transformation products (i.e., dissociation products, transformation products, valence states) and/or moieties of concern.[6]

When in contact with soil with clay content, linear polydimethylsiloxanes undergo siloxane bond redistribution and hydrolysis, resulting in the production of low molecular weight cyclic and linear oligomers (HSDB 2002). The resulting low molecular weight hydroxyl-functional hydrolysis products are water soluble, and the cyclic and trimethylsiloxy-end-blocked oligomers are volatile (HSDB 2002). Dimethylsilanediol (DMSD) (CAS #1066-42-8) and trimethylsilanol (CAS #1066-40-6) were identified as the primary degradation products in the environment (ECETOC 2011). As summarized in Table 4, both of these chemicals are identified as LT-U chemicals in the Pharos

[6] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

database. Based on the lack of significant hazards for these chemicals, the Benchmark Score for dimethicone is not adjusted by the transformation products.

Table 4. Transformation Product Summary Table

Functional Use	Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	Feasible and Relevant?	GreenScreen® List Translator Score or Benchmark Score[7,8]
NA	End	Hydrolysis	Dimethylsilanediol	1066-42-8	Yes	LT-U
NA	End	Hydrolysis	Trimethylsilanol	1066-40-6	Yes	LT-U

POTENTIAL CHEMICALS OF HIGH CONCERN

The GreenScreen® polymer criteria (CPA 2018b) require a Chemicals of High Concern (CoHC) analysis when any of the Group I human Health endpoints was assessed using Step 2c procedure (i.e., based on data on qualifying constituents or components), the final score for that endpoint is Moderate, Low or DG, and the residual monomer/catalyst of concern is present at 100 ppm or above.

No potential CoHC were identified as any residual monomer or catalyst are present in the polymer at <100 ppm (0.01%).

SPECIAL CASE IMPURITIES

Table 5. Special Case Impurities < 100 ppm in the Polymer Substance

Chemical Name	CASRN	(ppm)	GreenScreen® List Translator score	Function	Reason for Inclusion
Dimethyldichlorosilane	75-78-5	Not present (OECD 2010)	LT-P1	Monomer	Monomers < 100 ppm are considered special case impurities
Methanol	67-56-1	Not identified as impurity in cosmetic grade (CIR 2003)	BM-1	Reactant in manufacturing of starting materials	Identified as potential residual of manufacturing process
Unspecified copper catalyst	N/A	Not identified as impurity in cosmetic grade (CIR 2003)	N/A	N/A	Catalyst

TOXICOKINETICS

There was no evidence of absorption of dimethicone when an albino rat (weighing approximately 170 g) received oral administration of 0.58 g of an antifoam compound containing 28% [^{14}C]-dimethicone. Lactating dogs (weighing approximately 9 kg) orally administered 25 g of the antifoam compound had traces of siloxanes throughout the body. Authors estimated 0.0001% of the dose had been absorbed from the gastrointestinal (GI) tract (CIR 2003).

[7] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen® benchmark 1 chemicals (CPA 2012b). Pharos (Pharos 2015) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.

[8] The way you conduct assessments for transformation products depends on the Benchmark Score of the parent chemical (See Guidance).

When male Sprague-Dawley rats were administered a single oral dose of [^{14}C]-dimethicone fluid (either 35 or 1,000 cs) at 250 and 2,500 mg/kg, most of the material was detected in the GI tract at 4 and 8 hours after administration, with trace activity detected in the urine and scattered tissue samples at 8 hours. At 24 and 48 hours after administration, a majority of the material was detected in the feces and no activity was detected in tissues or organs at 48 hours (CIR 2003).

In a human study with two dimethicone antifoam preparations, six volunteers were given a single oral dose of 100 mg/kg of the two samples and five volunteers were given a single oral dose (100 mg/kg) of an emulsion (30 mg/kg solids) of the two samples. There were no significant increases in total or organosoluble urinary silicon and no organosilicon compounds were detected in expired air for the preparation containing <0.22% low-molecular weight polymers; however, the sample containing 10% low-molecular weight polymers contained 1.8% and 3.3% of the administered dose of the compound and emulsion, respectively, in the urine as an unidentified form of soluble organosilicon compound, and 0.25% of the given dose in the expired air primarily as octamethylcyclotetrasiloxane and small amounts of decamethylcyclopentasiloxane (CIR 2003).

A dermal absorption and distribution study applied an occlusive patch containing 332.5 kg/m·s [^{14}C]-dimethicone to male rats for 24 hours. Tracing results indicated 70% of the dose was recovered on the patch materials, 11.4% was present at the site of application, and none was found in the blood. Minimal amounts were found in the feces (0.01%) and carbon dioxide traps (0.001%) (CIR 2022).

In a dermal absorption study conducted in humans, five male volunteers received 50 mg/kg of 100 cs dimethicone fluid daily for 10 days for 20 hours. There was no significant test-related increase in blood and urine silicon concentrations in any of the subjects, and the authors concluded there was no evidence of dermal absorption of dimethicone (CIR 2003).

When beagle dogs (2/sex) were fed an antifoam compound containing 91% dimethicone at a dose of 300 mg/kg/day for 120 days, silicon was not detected in any organ, and fecal silicon output was approximately equal to the amount ingested; average output of urinary silicate was not increased (CIR 2003). Similarly, a male rhesus monkey orally administered 41.8 mg/kg of [^{14}C]-dimethicone (360 fluid) had virtually all radioactive label recovered in the feces. At 70.5 hours after dosing, 65.4% was recovered in the feces with an additional 27.3% of the dose recovered over the next hour as unchanged dimethicone (CIR 2003).

In summary, dimethicone was not absorbed by the oral and dermal routes in human and animal studies, although one study reported some oral absorption in humans for a low molecular weight dimethicone, which is outside the scope of this GreenScreen®.

HAZARD CLASSIFICATION SUMMARY

Note: Step 2 for classifying human health and ecotoxicity hazards of polymer consists of four separate sub steps. These are 2a: Use test data for polymer, 2b: Apply bridging principles for similar polymer, 2c: Apply hazard criteria for qualifying constituents or components and 2d: Apply expert judgment. See GreenScreen® Guidance v1.4, Figure 3 for more details.

GROUP I HUMAN HEALTH EFFECTS (GROUP I HUMAN)

Carcinogenicity (C) Score (H, M, or L): L

Dimethicone was assigned a hazard classification level of Low for carcinogenicity based on no increase in the incidence of benign or malignant tumors in long-term oral and dermal carcinogenicity

studies in rats and mice. GreenScreen® criteria classify polymers as a Low hazard for carcinogenicity when adequate data are available and negative and they are not GHS classified (CPA 2018b, Annex 7). Confidence in the score is high as it is based on reliable experimental data.

- **Polymer Substance (2a):**
  - ECETOC 2011, CIR 2022
    - *Oral:* A combined chronic toxicity and carcinogenicity study was performed with Fischer 344 rats (90/sex/dose group) provided diets containing silicone oil (10 cSt) at 0, 100, 300, or 1,000 mg/kg/day for 24 months. An interim sacrifice of 10 animals/sex/group occurred after 12 months of treatment. An additional 20 animals/sex/group were treated for 12 months, and then maintained for another 12 months without treatment. No increase in the incidence of benign or malignant tumors was observed with treatment.
    - *Oral:* In another carcinogenicity study, KS66 (a mixture of 92% dimethicone and 8% silica) was given to Fischer 344 rats (50/sex) at 0, 1.25%, or 5% for 104 weeks. The average KS66 intake in the 1.25% groups was 444.9 mg/kg (female) and 530.1 mg/kg (male) and 1,893.9 mg/kg (female) and 2,233.9 mg/kg (male) in the 5% groups, according to the study authors. No treatment related increase in the incidence of neoplastic or non-neoplastic lesions were observed in males or females of any dose group compared to controls. The authors concluded that KS66 was not carcinogenic.
  - CIR 2003
    - *Oral:* In an oral carcinogenicity study, male and female mice (50/sex, strain not reported) received diets of 0.25% or 2.5% dimethicone (91% purity) for 76 weeks. In a third group, mice received a single subcutaneous injection of dimethicone (0.2 mL) into the left flank. Silicone exposure was calculated to be 520 and 5,200 mg/kg/day for the 0.25% and 2.5% dose groups, respectively, and 201 mg for the subcutaneous injection group. Mice were sacrificed at 80 weeks. Males in the 0.25% diet group had an increased incidence of lymphoid hyperplasia, but the same was not noted in the 2.5% dose group and thus the authors did not consider this observation to be treatment related. A reduced incidence of uterine atrophy was noted in the females of the 2.5% dose group. No increase in the number of malignant or benign neoplasms was observed in any mice that received silicone in feed or via injection compared to controls. No additional details, including any on characterization of the test substance, were provided.
    - *Dermal:* In a dermal carcinogenicity study, a motor oil containing an unspecified amount of dimethicone was applied undiluted (50 µL) to the shaved skin of 50 male C3H/HeN mice were exposed twice weekly for life. Exposure sites were not covered. Once the survival rate for each group reached ≤ 10% the study was terminated. No application site neoplasms were found. No additional details, including any on characterization of the test substance, were provided.
- **Similar Polymer Substance (2b):**
  - Not applicable.
- **Qualifying Constituents (2c):**
  - Not applicable.
- **Professional Judgment (2d):**
  - No relevant information was identified.

- Based on the weight of evidence, a score of Low was assigned. The available oral and dermal studies in rats and mice found no evidence of carcinogenicity. Additionally, the mutagenicity and genotoxicity studies (discussed below in the mutagenicity/genotoxicity section) indicate that dimethicone is not carcinogenic, and repeated dose toxicity studies (discussed below in the repeated dose systemic toxicity/organ effects section) do not show evidence of systemic effects that may lead to carcinogenicity.

Mutagenicity/Genotoxicity (M) Score (H, M, or L): L

Dimethicone was assigned a hazard classification level of Low for mutagenicity/genotoxicity based on negative results in bacterial reverse mutation assays, mammalian cell transformation assays, a chromosome aberration assay, mammalian cell forward mutation assays, and two mouse micronucleus assays. GreenScreen® criteria classify polymers as a Low hazard for mutagenicity when adequate negative data are available for both gene mutations and chromosome aberrations and they are not GHS classified (CPA 2018b, Annex 7). Confidence in the score is high because it is based on consistently negative experimental genotoxicity data.

- **Polymer Substance (2a):**
  - ECETOC 2011
    - *In vitro*: Silicone oil (60,000 cSt, purity not reported) was evaluated in a bacterial mutagenicity assay (guideline and GLP-compliance not specified) with *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strains WP_2 *uvr*A and WP_2 *uvr*A (pKM 101) tested at up to 5,000 µg/plate with and without metabolic activation. In the first phase, precipitation was observed at ≥333 and ≥667 µg/plate, and in the second phase precipitation was observed at ≥500 and ≥1,500 µg/plate. No mutagenicity was reported.
    - *In vitro*: Silicone oil (350 cSt, purity not reported) in an emulsion in water with 10% Tween 80 was evaluated in a bacterial mutagenicity assay (guideline and GLP-compliance not specified) with *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 tested at up to 10 µL/plate with and without metabolic activation. There was no cytotoxicity at this dose, and there was no evidence of mutagenicity. Positive and negative controls were valid. Additional details, including details on characterization of the test substance, were not provided.
    - *In vitro*: Silicone oil (50 cSt, purity not reported) in water, alcohol, or DMSO was evaluated in a bacterial mutagenicity assay (guideline and GLP-compliance not specified) with *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 tested at 0.5, 10, 100, or 500 µL/plate with and without metabolic activation. There was no cytotoxicity at this dose, and there was no evidence of mutagenicity. Positive and vehicle controls were valid. Additional details, including details on characterization of the test substance, were not provided.
    - *In vitro*: Silicone oil (0.65, 100, and 1,000 cSt, purity not reported) was negative in a bacterial mutagenicity assay (guideline and GLP-compliance not specified) with *S. typhimurium* strains TA98, TA100, TA1535, TA1537 with and without metabolic activation. All test substances were negative. Additional details, including details on characterization of the test substance, were not provided.
  - CIR 2003
    - *In vitro*: Dimethicone was negative in twelve bacterial reverse mutation assays in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 and *E. coli*

strain WP_2 in the presence and absence of metabolic activation. In these assays dimethicone was tested as a mixture at 10% - 100% purity, a fluid at 100 and 1,000 cs, a mixture with unknown concentration, as a surfactant with 3% dimethicone, and as ethanol extractions of CU-7439 with < 0.1% dimethicone. Six studies reported dimethicone were tested at concentrations ranging from 0.5 – 5,000 µg/plate.

- *In vitro*: Dimethicone was negative in two mammalian cell transformation assays. BALB/C-3T3 mouse cells were treated with 500 – 10,000 µg/mL Q7-2059 or Q7-2167/68 gel (79% purity) in the presence and absence of metabolic activation.
- *In vitro*: Dimethicone was negative in a chromosome aberration assay. Chinese hamster ovary (CHO) cells were treated with Q7-2167/68 gel (79% dimethicone) at concentrations of 625, 1,250, 2,500, 5,000, and 10,000 µg/mL in the presence and absence of metabolic activation .
- *In vitro*: Dimethicone was negative in two CHO/HGPRT forward mutation assays. CHO cells were tested with Q7-2159A or Q7-2167/68 gel (79% dimethicone) at concentrations of 312.5, 625, 1,250, 2,500, 5,000, and 10,000 µg/mL in the presence and absence of metabolic activation.
- *In vivo:* Dimethicone was negative in a micronucleus test using Swiss/Webster mice. Mice (5/sex) received a single intraperitoneal injection of 5 g/kg Q7-2159A gel (79% dimethicone). Peripheral blood samples were collected at 24, 48, and 72 hours and micronuclei per 1,000 polychromatic erythrocytes were counted. No evidence of genotoxicity was found.
- *In vivo*: Dimethicone was negative in a micronucleus test using CD-1 mice. Mice (5/sex) received a single intraperitoneal injection of 1.25, 2.0, and 2.5 g/kg Q7-2167/68 gel (79% dimethicone). Peripheral blood samples were collected at 24, 48, and 72 hours and micronuclei were counted. No evidence of genotoxicity was found (CIR 2003).

- **Similar Polymer Substance (2b):**
  - Not applicable.
- **Qualifying Constituents (2c):**
  - Not applicable.
- **Professional Judgment (2d):**
  - No relevant information was available.

Reproductive Toxicity (R) Score (H, M, or L): *L*

Dimethicone was assigned a hazard classification level of Low for reproductive toxicity based on a lack of effects on reproductive organ weights and sperm parameters in oral and dermal studies, and a lack of effects on mating in an implantation study. GreenScreen® criteria classify polymers as a Low hazard for mutagenicity when adequate data are available and negative and they are not GHS classified (CPA 2018b, Annex 7). Confidence in the score is low due to observations from a limited number of parameters, limited number of animals, and/or limited duration in what appears to be non-guideline studies and due to uncertainty regarding the relevance of the implantation study.

- **Polymer Substance (2a):**
  - CIR 2003
    - In a study designed to investigate the possible atrophic changes in rat seminal vesicles following oral exposure to dimethicone, Sprague-Dawley rats (10 males) were administered three dimethicone-containing fluids at 3.3 mL/kg/day

(equivalent to 3,102 mg/kg/day[9]) for 6 days via gavage. One dimethicone fluid (TX-158X) produced a significant reduction in the average seminal vesicle to body weight ratio, but not in absolute organ weight. No adverse effects were found in the two other samples.

- ECETOC 2011
  - Male Sprague-Dawley rats (10/dose group) were administered oral doses of dimethicone (250 cST) at 0 or 1,000 mg/kg/day 5 days/week for 4 weeks. The animals were evaluated for body weights, food consumption, and organ weights (testes, epididymides, prostate). No treatment-related effects were reported on these parameters.
  - Male albino rabbits (5/dose group) were administered dermal doses of dimethicone (350 cSt) at approximately 3,000 mg/kg/day for 5 days/week for 4 weeks. The animals were evaluated for body weights, semen quality (volume, viscosity, color), and organ weights (testes, epididymides). No treatment-related effects were reported on these parameters.
  - Charles River CD rats (30/sex/dose group) were implanted with a cross-linked dimethicone gel resulting in exposures of 2,800, 9,500 or 28,500 mg/kg. Prior to mating, males were treated for 61 days and females were treated for 47 days. The female parental animals were evaluated for body weights, gross necropsy (gestational day (GD) 20 or day 21 post-delivery), and histopathology. The offspring were evaluated for weight, sex, litter size, incidence of still births and external malformations, survival, growth, and nursing behavior. No treatment-related effects were reported on these parameters.

- **Similar Polymer Substance (2b):**
  - Not applicable.
- **Qualifying Constituents (2c):**
  - Not applicable.
- **Professional Judgment (2d):**
  - No relevant information was available.
- Based on the weight of evidence, a score of Low was assigned. One oral study involving a high daily dose of > 3,000 mg/kg/day for 6 days in rats reported seminal vesicle atrophy. However, this dose is higher than the limit dose of 1,000 mg/kg/day in current OECD guidelines for reproductive and developmental toxicity studies. Information on the characterization of the tested dimethicone was not available. In contrast, other oral and dermal studies at up to 3,000 mg/kg/day for up to 4 weeks demonstrate a lack of effects on reproductive organ and sperm parameters, and an implantation study demonstrates a lack of effects on mating and reproduction at doses up to 28,500 mg/kg/day. Although the implantation route of exposure is not a route typically considered in a GreenScreen®, it supports a lack of effects on reproductive parameters.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): L
Dimethicone was assigned a hazard classification level of Low for developmental toxicity based on the absence of adverse effects in rat and rabbit developmental toxicity studies. GreenScreen® criteria classify polymers as a Low hazard for developmental toxicity when adequate data are available and negative and they are not GHS classified (CPA 2018b, Annex 7). Confidence in the score is high as it is based on reliable experimental data.

[9] 3.3 mL/kg/day * 0.94 g/cm^3 * 1,000 mg/g = 3,102 mg/kg/day

- **Polymer Substance (2a):**
  - CIR 2003
    - *Oral:* In a developmental toxicity study, pregnant Wistar rats (number not reported) were administered a medical grade antifoam compound containing 93% dimethicone on GD 6 – 15 at doses of 0.38, 1.20, and 3.80 g/kg/day. The highest dose of 3.80 g/kg/day represents 70 times the recommended clinical dose for the treatment of intestinal gas and 1,000 times the dose recommended to treat peptic ulcers. Treatment caused no significant differences in fetal viability, resorptions, fetal average weight, and gross external, soft tissue, and skeletal anomalies. ToxServices identified a developmental NOAEL of 3.8 g/kg/day (equivalent to 3,534 mg/kg/day[10] dimethicone) based on the absence of adverse effects.
    - *Oral:* In a developmental toxicity study, pregnant New Zealand white rabbits (number not reported) were fed a diet containing 0, 0.5, 1.0, or 2.5% food grade dimethicone on GDs 6 to 19. No maternal toxicity was reported. Treatment had no effect on the incidence of resorptions, pup weight, or the incidence of external, visceral, or skeletal abnormalities. ToxServices identified a developmental NOAEL of 2.5% dimethicone (equivalent to 806.5 mg/kg/day[11]).
    - *Dermal:* In a developmental toxicity study, groups of fifteen pregnant rabbits (strain not reported) were dermally exposed to 200 mg/kg dimethicone (medical grade fluid, 350 cs; suspended in corn oil or sesame oil in a 1:5 ratio) on GDs 6 to 18. A separate group received subcutaneous injections of 20, 200, or 1,000 mg/kg dimethicone. Litters were delivered by caesarean section on day 29. No treatment-related effects were found. ToxServices identified a developmental NOAEL of 200 mg/kg for the dermal applications, the only dose tested, and 1,000 mg/kg dimethicone for the subcutaneous injection.
  - ECETOC 2011
    - A prenatal developmental toxicity study was performed with female New Zealand White rabbits (number not specified) implanted with a dimethicone gel (purity not reported) 6 weeks prior to insemination. The dose levels were 2,850, 9,500, or 28,500 mg/kg. The animals were sacrificed on GD 29. The dams were evaluated for body weights, clinical signs of toxicity, and uterine/ovarian content. The offspring were evaluated for sex, viability, and the presence of external, visceral, and skeletal malformations. No treatment-related effects were reported on these parameters.
    - *Oral:* A prenatal developmental toxicity test was performed with pregnant female New Zealand White rabbits (23/dose group) administered oral doses of dimethicone (350 cSt, purity not reported) at 0, 33, 300, or 1,000 mg/kg/day via gavage on GDs 6-19. No treatment-related effects on reproductive performance or the type or incidence of abnormalities were reported with treatment. The study authors identified a developmental toxicity NOAEL of 1,000 mg/kg/day.
  - HSDB 2002
    - A developmental toxicity study was performed with pregnant female rats (20 total, strain not specified) administered subcutaneous injections of dimethicones (purity not specified) in sesame oil at 20, 200, or 1,000 mg/kg on unspecified

[10] 3.8 g/kg/day * 0.93 = 3.534 g/kg/day or 3,534 mg/kg/day

[11] 2.5% = 25,000 mg/kg feed * 0.100 kg food/day / 3.10 kg = 806.5 mg/kg/day. Dose was calculated using default values for female New Zealand White rabbits, subchronic study (U.S. EPA 1988).

days of gestation. A slight increase in delayed ossification of the sternebrae and cranial bones was observed in the high dose group.
    - Although the subcutaneous injection route is not a typical route of exposure for GreenScreen® hazard assessments, the above study indicates that developmental effects were only observed at high doses (1,000 mg/kg). Similar effects will only be observed at higher doses administered via the oral, dermal, or inhalation routes due to the limited absorption and distribution for polymers like dimethicone.
- **Similar Polymer Substance (2b):**
    - Not applicable,
- **Qualifying Constituents (2c):**
    - Not applicable.
- **Professional Judgment (2d):**
    - No relevant information was available.

Endocrine Activity (E) Score (H, M, or L): DG
Dimethicone was assigned a hazard classification level of Data Gap for endocrine activity based on a lack of data for the polymer and lack of qualifying constituent data to support classification.
- **Polymer Substance (2a):**
    - No data were identified.
- **Similar Polymer Substance (2b):**
    - Not applicable.
- **Qualifying Constituents (2c):**
    - *Octamethylcyclotetrasiloxane (CAS #556-67-2[12]):*
        - Pharos 2023
            - *Screening:* EU - Priority Endocrine Disrupters (EU ED): Category 1 - In vivo evidence of endocrine disruption activity
            - *Screening:* ChemSec - Substitute List (SIN): Equivalent concern, including endocrine disruption - Sin List 1.0
            - *Screening:* TEDX - Potential Endocrine Disruptors (TEDX): Potential Endocrine Disruptor
        - Dekant et al. 2017
            - The ability of octamethylcyclotetrasiloxane to interact with endocrine pathways was assessed in a series of experiments. These are briefly summarized below:
                - In an *in vivo* uterotrophic assay, octamethylcyclotetrasiloxane possesses only very weak estrogenic and antiestrogenic activity in rats and has a low affinity for estrogen receptor-α, five to six orders of magnitude below that of the positive control ethinylestradiol.
                - In a two-generation reproductive and developmental study with octamethylcyclotetrasiloxane, no estrogenic/antiestrogenic activity on pubertal timing in male or female rats was seen.

[12] This qualifying constituent is evaluated under this endpoint because it is present above 0.1% and no data are available for the polymer substance or a similar polymer substance.

    - Octamethylcyclotetrasiloxane did not show androgenic activity in the Herschberger assay with male F344 rats through whole body inhalation.
    - In *in vitro* ligand binding assays including assessment of receptor binding to calf uterine progesterone receptor and to recombinant human progesterone receptor (alpha and beta forms), there was no indication of binding of octamethylcyclotetrasiloxane to the progesterone receptor.
    - No activation of recombinant human progesterone receptor-β was seen in a cell-based reporter gene assay.
    - Based on the above, authors concluded that D4 has weak estrogenic/antiestrogenic activity and this very weak activity of octamethylcyclotetrasiloxane in estrogenic assays is unlikely to be responsible for the increase in the endometrial proliferative lesions seen in a 2-year chronic bioassay.
- The qualifying constituent octamethylcyclotetrasiloxane warrants a Moderate score for endocrine activity. Octamethylcyclotetrasiloxane is present on the three screening lists, TEDX - Potential Endocrine Disruptors, EU - Priority Endocrine Disrupters (Category 1) and ChemSec – SIN list, which corresponds to a score of Moderate to High. Available experimental data indicated that octamethylcyclotetrasiloxane has weak estrogenic/antiestrogenic activity. According to GreenScreen® guidance, a chemical should be assigned a Moderate hazard if there is an indication of endocrine activity in the scientific literature, and only when there is a plausible related adverse effect for carcinogenicity, reproductive toxicity, developmental toxicity, and/or systemic toxicity (repeated dose) that corresponds to a High hazard should the hazard level be modified from a Moderate to High. The hazards for octamethylcyclotetrasiloxane have been reviewed elsewhere in a previous GreenScreen® by ToxServices (ToxServices 2018). The very weak activity of octamethylcyclotetrasiloxane in estrogenic assays is unlikely to be responsible for an increase in the endometrial proliferative lesions seen in a 2-year chronic bioassay. In terms of systemic toxicity and reproductive toxicity, octamethylcyclotetrasiloxane was assigned a score of Moderate based on reproductive effects seen in female rats, changes in relative liver and kidney weights, and chronic nephropathy. However, these effects as discussed in great details by Dekant et al are not mediated through endocrine activity, and therefore, the preliminary Moderate score was not modified to High.
- *Decamethylcyclopentasiloxane (CAS #541-02-6)* [13]*:*
    - Pharos 2023
        - *Screening:* TEDX - Potential Endocrine Disruptors (TEDX): Potential Endocrine Disruptor
    - ECHA 2023, SCCS 2015, EC 2008
        - *Inhalation:* In a GLP-compliant 2-generation reproductive and developmental toxicity study that was conducted according to EPA OPPTS 870.3800 (Reproduction and Fertility Effects)/EPA OPP 83-6 (Developmental Neurotoxicity Study), male and female Sprague-Dawley rats were exposed via whole body inhalation to decamethylcyclo-pentasiloxane (>99% purity) at concentrations of 0, 30, 70, or 160 ppm

[13] This qualifying constituent is evaluated under this endpoint because it is present above 0.1% and no data are available for the polymer substance or a similar polymer substance.

(0.478, 1.094, or 2.496 mg/L) for 6 hours/day, 7 days/week for at least 70 days prior to mating, through mating and gestation day 20, and through lactation with the exception of days 0-4 (both F0 and F1 generations). Offspring for mating (30/sex/dose) were selected at 21 days of age and were mated at 13-15 weeks of age. The F1 pups were exposed from weaning through sexual maturity, breeding, and gestation. Developmental landmarks (balanopreputial separation and vaginal patency) were evaluated in these rats. Pups of the F2 generation (30/sex/dose) were also evaluated for developmental landmarks. Anogenital distance was slightly but statistically significantly increased in male pups at the high dose (not evaluated in other dose groups). The Scientific Committee on Consumer Safety (SCCS) noted that an increase in male pup anogenital distance may indicate an anti-estrogenic or androgenic effect, but other studies have not shown such activity for decamethylcyclopentasiloxane and vaginal patency and balanopreputial separation were not affected.

- *Inhalation*: In a subacute inhalation study that was designed to evaluated effects on liver and thyroid cell proliferation and liver hypertrophy, female Fischer 344 rats (30/dose) were exposed to decamethylcyclopentasiloxane (purity not reported) vapors at concentrations of 0 of 160 ppm (2.496 mg/L) 5 days/week for 28 days (hours of exposure not reported). Animals (10/dose) were sacrificed on days 0, 7, and 21 and histopathological evaluations were conducted on the thyroid/parathyroid. There were no clinical signs of toxicity. There was a slight (< 2-fold) but statistically significant increase in the incidence of thyroid hyperplasia after the second and fourth 5-day exposure periods.

▪ SCCS 2015
- "A series of studies have also been conducted to investigate the potential estrogenic, androgenic and progestatic activity of D5 (Ref 101-106). These studies showed that D5 has no direct estrogenic, anti-estrogenic, androgenic, anti-androgenic or progestagenic activity."

▪ EC 2008
- Decamethylcyclopentasiloxane did not increase uterine wet or blotted weights or in uterine epithelial cell height in SD and F344 rats exposed via inhalation to 2.4 mg/L for 16 hours/day for three days. Environment Canada concluded that the substance was negative for estrogenic activity.
- Decamethylcyclopentasiloxane was negative in a Hershberger assay. There was no increase in reproductive organ weights in F344 rats exposed via inhalation to 2.4 mg/L for 16 hours/day for ten days. Environment Canada concluded that the substance was negative for androgenic activity.
- *In vitro*, decamethylcyclopentasiloxane human estrogen receptor α (Erα) or estrogen receptor β (Erβ), and was negative in an Erα reporter gene assay in a human epithelial cell line MCF-7. It also showed no binding affinity to progesterone receptors (PRs) and was negative in a PRβ reporter gene assay.

o The qualifying constituent decamethylcyclopentasiloxane warrants a Data Gap for endocrine activity. ToxServices did not consider a < 2-fold increase in thyroid

hyperplasia to be biologically significant, and this effect was not considered by the SCCS to be of toxicological significance. The SCCS also noted that the relevance of a slight increase in male pup anogenital distance was uncertain considering the lack of effects on other endpoints and in several additional endocrine assays. The SCCS concluded that there is no evidence of a direct interaction with the endocrine system based on available data. However, very limited data are available to evaluate the thyroid or other pathways apart from the androgen/estrogen pathways and therefore a Data Gap was assigned.

- **Professional Judgment (2d):**
  - No relevant information was available.
- Based on a weight of evidence evaluation, a Data Gap was assigned. As no data are available for the polymer or similar polymer substance, qualifying constituents were evaluated. Of these constituents, octamethylcyclotetrasiloxane received the worst score of Moderate. According to GreenScreen® criteria for polymer constituents/components described in Annex 8, qualifying constituents with evidence of endocrine activity (i.e., a score of Moderate for the qualifying constituent) warrant classification of the polymer as Moderate when the qualifying constituent is present at or above 1%. As octamethylcyclotetrasiloxane is present at less than 1%, it does not impact the classification of the polymer. Therefore, a Data Gap was assigned.

GROUP II AND II* HUMAN HEALTH EFFECTS (GROUP II AND II* HUMAN)
Note: Group II and Group II endpoints are distinguished in the v1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. See GreenScreen® Guidance v1.4, Annex 2 for more details.*

Acute Mammalian Toxicity (AT) Score (vH, H, M, or L): L
Dimethicone was assigned a hazard classification level of Low for acute toxicity based on several oral and dermal LD_{50} values exceeding 2,000 mg/kg and an LC_{50} of >11.582 mg/L. GreenScreen® criteria classify polymers as a Low hazard for acute toxicity when oral and dermal LD_{50} values are greater than 2,000 mg/kg and inhalation LC_{50} values are greater than 5 mg/L, and they are not GHS classified (CPA 2018b, Annex 7). Confidence in the score is high as it is based on reliable data from several studies.

- **Polymer Substance (2a):**
  - ECETOC 2011
    - *Oral:* LD_{50} >4,800 mg/kg (species not specified)
  - ECETOC 2011, CIR 2022
    - *Inhalation:* 4-hour LC_{50} > 4.315 mg/L (MMAD 1.55 µm) and > 11.582 mg/L (MMAD 0.846 µm) (Wistar rat) (OECD Guideline 403)
    - *Inhalation:* 4-hour LC_{50} > 0.695 mg/L with polydimethylsiloxane mist (MMAD up to 1.8 µm) (Wistar rat)
  - HSDB 2017
    - *Oral:* LD_{50} > 20,000 mg/kg (mouse)
    - *Dermal:* LD_{50} > 2,008 mg/kg (rat)
    - *Dermal:* A commercial emulsion containing 15% dimethicone had an LD_{50} of 16 mL/kg in rabbits (equivalent to 2,256 mg/kg[14]).
  - CIR 2003
    - Numerous acute oral toxicity studies in mice, rats, and guinea pigs found dimethicone to have low acute toxicity. Oral LD_{50} values of > 10 mg/kg (35%

[14] 16 mL/kg * 0.94 g/cm^3 * 1,000 mg/g = 15,040 mg/kg * 0.15 = 2,256 mg/kg

dimethicone, equivalent to 3,290 mg/kg[15]) in mice, up to 31.9 g/kg (85% dimethicone, equivalent to 27,370 mg/kg[16]) in rats, and up to > 30 g/kg (35% dimethicone, equivalent to 10,500 mg/kg[17]) in guinea pigs were identified.
    - CIR 2003, 2022
        - *Oral:* LD_{50} > 2,000 mg/kg (rats and rabbits)
- **Similar Polymer Substance (2b):**
    - Not applicable.
- **Qualifying Constituents (2c):**
    - Not applicable.
- **Professional Judgment (2d):**
    - No relevant information was available.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single) Score (H, M, or L): L
Dimethicone was assigned a hazard classification level of Low for single dose systemic toxicity/organ effects based on a lack of indications of systemic toxicity in several oral, dermal, and inhalation acute toxicity studies. GreenScreen® criteria classify polymers as a Low hazard for single dose systemic toxicity/organ effects when there is no systemic toxicity below the oral and dermal guidance value of 2,000 mg/kg and the inhalation guidance value of 5 mg/L and they are not GHS classified (CPA 2018b, Annex 7). Confidence in the score is high as it is based on reliable experimental data.

- **Polymer Substance (2a):**
    - HSDB 2017
        - Dogs (2), guinea pigs (7), and rats (7) were exposed to an aerosol containing an unspecified concentration of dimethicone for 6 hours. Hyperventilation, excitability and salivation were noted during exposure. Hyperemic lungs, edema, hemorrhage and mild irritation of the lungs were found upon necropsy. No additional details were provided.
            - As the concentration of dimethicone is unknown, insufficient information is available for assigning a score.
    - ECETOC 2011
        - *Oral*: In an acute oral toxicity study that identified an oral LD_{50} greater than 4,800 mg/kg in Wistar rats (5/sex) dosed with silicone oil (1,000 cst), no clinical signs of toxicity, changes to body weight, or gross pathological findings were reported with treatment.
    - ECETOC 2011, CIR 2003
        - *Oral*: In an acute oral toxicity study that identified an oral LD_{50} greater than 2,000 mg/kg in Sprague-Dawley rats (5/sex) dosed with silicone oil (60,000 cst) via gavage, no clinical signs of toxicity, changes to body weight, or gross pathological findings were reported with a gavage treatment.
    - ECETOC 2011, CIR 2022
        - *Dermal*: In an acute dermal toxicity study that identified a dermal LD_{50} greater than 2,000 mg/kg in New Zealand White rabbits (5/sex) treated with silicone oil (60,000 cSt), erythema was observed in all 10 animals included in the study. No

[15] 10 mL/kg * 0.94 g/cm^3 * 1,000 mg/g = 9,400 mg/kg * 0.35 = 3,290 mg/kg
[16] 31.9 g/kg * 0.858 = 27.4 g/kg * 1,000 mg/g = 27,370 mg/kg
[17] 30 g/kg * 0.35 = 10.5 g/kg * 1,000 mg/g = 10,500 mg/kg

treatment-related changes to body weight or gross pathological findings were reported following occlusive application for 24 hours.
    - *Dermal*: In an OECD Guideline 402 acute dermal toxicity study that identified a dermal LD_{50} greater than 2,008 mg/kg in Sprague-Dawley rats treated with silicone oil (350 cSt), no treatment-related clinical signs of toxicity, changes to body weight, or gross pathological findings were reported following occlusive application for 24 hours.
    - *Inhalation*: In an OECD Guideline 403 acute inhalation toxicity study that identified a 4-hour inhalation LC_{50} greater than 11.582 mg/L in Wistar rats (5/sex), no clinical signs of toxicity were observed during the exposure or observation periods and no gross pathological findings were reported following nose-only exposure to dimethicone dissolved in petroleum ether (100,000 cSt).
    - *Inhalation*: In an OECD Guideline 403 acute inhalation toxicity study that identified a 4-hour inhalation LC_{50} greater than 0.695 mg/L in Wistar rats (5/sex), no clinical signs of toxicity were observed during the exposure or observation periods, no changes to body weight, and no gross pathological findings were following exposure to dimethicone dissolved in dichloromethane (10,000 cSt).
- **Similar Polymer Substance (2b):**
    - Not applicable.
- **Qualifying Constituents (2c):**
    - Not applicable.
- **Professional Judgment (2d):**
    - No relevant information was identified.
- Based on the weight of evidence, a score of Low was assigned. Several acute oral and dermal studies report a lack of effects on clinical signs, body weights, and gross pathology. Although one inhalation study reported clinical effects potentially indicative of respiratory irritation, the concentrations were not reported and two additional studies showed no evidence of respiratory irritation.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-repeat) (Group II*) Score (H, M, or L): L

Dimethicone was assigned a hazard classification level of Low for repeated dose systemic toxicity/organ effects based on a lack of systemic effects in several oral repeated dose toxicity studies in rats, mice, rabbits, and dogs below the guidance value of 100 mg/kg/day and in a dermal 28-day study in rabbits below the adjusted guidance value of 600 mg/kg/day. GreenScreen® criteria classify polymers as a Low hazard for repeated dose systemic toxicity/organ effects when there is no evidence of systemic toxicity below the oral and dermal guidance values of 100 and 200 mg/kg/day, respectively, for 90-day studies (CPA 2018b, Annex 7). Confidence in the score is high as it is based on reliable experimental data.

- **Polymer Substance (2a):**
    - CIR 2003
        - *Oral:* In a 90-day oral toxicity study, male and female Sprague-Dawley rats (10/sex) were administered a diet containing 1% dimethicone at 5 different viscosities (30, 350, 1,000, 10,000, and 60,000 cSt). There were no effects on food consumption, weight gain, hematological parameters, organ weights, and microscopic parameters.

- ToxServices identified a NOAEL of 1% dimethicone (equivalent to 860 and 980 mg/kg/day in males and females, respectively[18]) which was the only dose tested.

- *Oral:* In a 90-day study, male and female rats (strain not specified, 10/sex/group) were fed 0.1% or 1% of a diet containing 91% dimethicone. Following the 90-day treatment rats were fed a control diet for 2 weeks and then necropsied. No clinical pathology or microscopic changes were reported.
  - ToxServices identified a NOAEL of 1% (equivalent to 873.6 mg/kg/day[19]), which was the highest dose tested.
- *Oral:* In a 90-day study, groups of six dogs (3/sex/group) were fed an antifoam compound containing 95% dimethicone at 120, 380, or 1,200 mg/kg/day. Treatment had no effect on blood chemistry, hematology, or pathology.
  - ToxServices identified a NOAEL of 1,200 mg/kg/day (equivalent to 1,140 mg/kg/day dimethicone[20]) which was the highest dose tested.
- *Oral:* In a 4-week oral toxicity study, rats (strain and number not reported) were fed a diet containing 0.04% linear/cyclic dimethylpolysiloxanes or 5% linear/cyclic dimethylpolysiloxanes. Treatment had no effect on body weight, organ weight, or oxygen consumption.
  - ToxServices identified a NOAEL of 5% (equivalent to 4,800 mg/kg/day[21]), which was the highest dose tested.
- *Oral:* In a 90-day study, CD-1 mice (15/sex/group) were fed diets containing 5% or 10% dimethicone fluid. Treatment had no effect on body or organ weight. No microscopic lesions were found.
  - ToxServices identified a NOAEL of 10% (equivalent to 19,700 mg/kg/day dimethicone[22]), which was the highest dose tested.
- In a 90-day study, Sprague-Dawley rats (20/sex/group) were fed a diet containing 1%, 5%, or 10% dimethicone at one of three viscosities, 35, 350, and 1,000 cSt. No treatment-related toxicity was observed.
  - ToxServices identified a NOAEL of 10% (equivalent to 8,600 and 9,800 mg/kg/day in males and females, respectively[23]), which was the highest dose tested.
- *Oral:* In a 90-day study, male Sprague-Dawley rats (100/group) were fed 10% dimethicone fluid at one of three viscosities (35, 350, and 1,000 cs). No treatment-related signs of toxicity were found. Treatment had no effect on body weight, hematology, or histopathology.

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[18] 1% = 10,000 mg/kg * 0.086 kg food/kg BW/day = 860 mg/kg/day (males) and 1% = 10,000 mg/kg * 0.098 kg food/kg BW/day = 980 mg/kg/day (females). Dose was calculated using the male and female Sprague-Dawley rat food factor values for a subchronic study (TERA Undated).

[19] 1% = 10,000 mg/kg * 0.096 kg food/kg BW/day = 960 mg/kg/day * 0.91 = 873.6 mg/kg/day. Dose was calculated using the male and female rat average food factor value for a subchronic study (TERA Undated).

[20] 1,200 mg/kg/day * 0.95 = 1,140 mg/kg/day

[21] 5% = 50,000 mg/kg * 0.096 kg food/kg BW/day = 4,800 mg/kg/day. Dose was calculated using the male and female rat average food factor value for a subchronic study (TERA Undated).

[22] 10% = 100,000 mg/kg * 0.197 kg food/kg BW/day = 19,700 mg/kg/day. Dose was calculated using the male and female mouse average food factor value for a subchronic study (TERA Undated).

[23] 10% = 100,000 mg/kg * 0.086 kg food/kg BW/day = 8,600 mg/kg/day in males and 100,000 mg/kg * 0.098 kg food/kg BW/day = 9,800 mg/kg/day in females. Doses were calculated used male and female rat food factor values for subchronic studies (TERA Undated).

- ToxServices identified a NOAEL of 10% (equivalent to 8,600 mg/kg/day in males[24]), which was the only dose tested.

- *Oral:* In a subchronic oral toxicity study, rats (strain and number not reported) were fed an antifoam compound containing 83% dimethicone at concentrations of 0.1%, 0.3%, or 1.0% for 120 days. Treatment had no effect on growth, appearance, behavior, mortality, hematologic parameters, or blood urea nitrogen were observed. While spleen and liver weights were reportedly increased in high dose animals, the significance of this finding is unclear due to lack of details (e.g., magnitude of the effect, absolute or relative weights, microscopic findings). ToxServices conservatively identified a NOAEL of 0.3% (equivalent to 239 mg/kg/day[25]).
- *Oral:* In a chronic toxicity study, dimethicone was administered in the diet of rats (strain and number not reported) (1 year treatment) and rabbits (strain and number not reported) (8 month treatment) at 1%. No treatment-related effects were found at necropsy.
    - ToxServices identified a NOAEL of 1% (equivalent to 780 mg/kg/day in rats and 319 mg/kg/day in rabbits[26]), which was the only dose tested.
- *Oral*: In a previously described oral carcinogenicity study, mice (strain not reported, 50/sex) were fed an antifoam compound containing 91% dimethicone at 0.25% or 2.5% for 76 weeks. A separate group received a subcutaneous injection of the test material (0.2 mL) into the left flank. Mice were killed at 80 weeks. CIR reported that exposure to the polymer was estimated at 520 and 5,200 mg/kg/day for the oral study and 201 mg/kg/day for the subcutaneous study. Survival was decreased in females in the oral high dose group, but the change was not statistically significant when deaths attributed to cage flooding were excluded. In the low dose oral group, males had an increased incidence of superficial ulceration of the stomach and females had an increased incidence of lymphoid hyperplasia, but authors did not consider these effects toxicologically relevant as they were not reported in the high dose group. There were no increases in benign neoplasms. In the subcutaneous injection group, the only effects were injection site cysts and hair loss. No data on additional systemic toxicity endpoints were reported, and no additional details, including any on characterization of the test substance, were provided.
- *Inhalation:* A cat, rabbit, guinea pig, 2 rats, and 4 mice were sprayed for 4 hours per day with an atomizer containing 10 ml/kg of a sample of dimethicone (140 cm^2/s, purity not specified) for 29 days. During the 6 week observation period, no exposure related adverse effects were seen in the cat, rabbit, guinea pig, or rats; however, all 4 mice died (one during the dosing period and the other three during the post-dosing period). The link between the treatment and death

[24] 10% = 100,000 mg/kg * 0.086 kg food/kg BW/day = 8,600 mg/kg/day in males. Dose was calculated used the male Sprague-Dawley rat food factor value for subchronic studies (TERA Undated).

[25] 0.3% = 3,000 mg/kg * 0.096 kg food/kg BW/day = 288 mg/kg/day * 0.83 = 239 mg/kg/day. Dose was calculated using male and female rat average food factor values for subchronic studies (TERA Undated).

[26] 1% = 10,000 mg/kg * 0.078 kg food/kg BW/day = 780 mg/kg/day in rats. Dose was calculated using male and female rat average food factor values for chronic studies (TERA Undated).
1% = 10,000 mg/kg food * 0.12 kg food / 3.76 kg = 319 mg/kg/day in rabbits. Dose was calculated using the default food and weight factors for male New Zealand rabbits for chronic studies (U.S. EPA 1988).

observed in mice was uncertain and the study authors concluded that inhalation to dimethicone is considered harmless.

- Due to the small number of animals, lack of controls, and limited study details, ToxServices did not consider this study reliable, and it is therefore excluded from the weight of evidence.

- CIR 2003, 2022
  - *Oral:* In a subchronic oral toxicity study, two mongrel dogs were fed an antifoam compound containing 83% dimethicone at 0.3, 1.0, or 3.0 g/kg/day in ground horse meat 5 days per week for 3 months. Control animals received untreated horse meat. Following 3 months of treatment, dogs were fed a commercial dog food for 3 months. Dogs in the high dose group had a thin layer of viscid, gray material covering the intestinal tract and enlarged lymphoid aggregates of the small intestine. Pigment deposits were observed in the liver and found to be bile; quantities were dose-related.
    - ToxServices identified a LOAEL of 0.3 g/kg/day (equivalent to 177.9 mg/kg/day[27]) based on effects on the liver but notes the small number of animals per dose may affect statistical reliability (e.g., OECD Guideline 452 and FDA Redbook 2000 recommend at least 4 dogs/sex/group (OECD 2018, U.S. FDA 2003)).
  - *Oral:* In a 2-year study, male and female Wistar rats (25/sex) were fed a diet containing 0.3% of a dimethicone-containing compound (percent dimethicone not specified). Treated rats had increased weight gain compared to controls, and at microscopic examination, pulmonary lesions, changes in ovaries and uterus, and mild fatty changes in liver and tubular epithelium of kidney were observed in all treated rats. No further details were provided.
    - ToxServices determined that the LOAEL was 0.3% (equivalent to 222 mg/kg/day for males and 252 mg/kg/day for females[28], assuming 100% dimethicone). A NOAEL could not be established due to the use of only one dose.
- ECETOC 2011
  - *Oral:* A 90-day repeated dose toxicity study was performed with Sprague-Dawley rats (10/sex/group) provided diets containing silicone oil (35, 350, or 1,000 cSt) at 1, 5, or 10% (10,000 to 100,000 ppm). The animals were evaluated for clinical signs of toxicity, body weight, food consumption, gross pathology, and histopathology. No treatment-related effects were observed on these parameters and the study authors identified a NOAEL of 100,000 ppm (equivalent to 8,600 and 9,800 mg/kg/day for males and female, respectively[29])
  - *Oral:* A 13-week repeated dose toxicity study was performed with Fischer 344 rats (15/sex/dose group) provided diets containing silicone oil (10 cSt) at 10,000 to 50,000 ppm. The animals were evaluated for clinical signs of toxicity, body weight, food consumption, hematology, clinical chemistry, urinalysis, gross

[27] 0.3 g/kg/day * 0.83 * 5 days/7 days = 0.1779 g/kg/day or 177.9 mg/kg/day

[28] 0.3% = 3,000 mg/kg feed * 0.074 kg feed/kg bw/day = 222 mg/kg/day in males and 0.3% = 3,000 mg/kg feed * 0.084 kg feed/kg bw/day = 252 mg/kg/day in females. Doses were calculated using male and female Wistar rat food factor for chronic toxicity study (TERA Undated).

[29] 100,000 mg/kg * 0.086 kg food/kg BW/day = 8,600 mg/kg/day (males) and 100,000 mg/kg * 0.098 kg food/kg BW/day = 9,800 mg/kg/day (females). Dose was calculated using the male and female rat food factor values for a subchronic study (TERA Undated).

pathology, and histopathology. An increased matting of fur was observed at 25,000 and 50,000 ppm in males and females. Direct contact of the material with fur and eyes resulted in corneal opacity and inflammation with vascularization. No treatment-related effects were observed on body weight, hematology parameters, urinalysis parameters, organ weights, gross pathology, or histopathology. High density lipoprotein, cholesterol, and phospholipid levels decreased in all treated males, but the ECETOC authors did not consider them to be adverse effects. The study authors identified a NOAEL of 50,000 ppm (equivalent to 5,000 and 5,650 mg/kg/day in males and females, respectively[30]) based on the lack of systemic toxic effects observed in this study.

- *Oral*: A combined chronic toxicity and carcinogenicity study was performed with Fischer 344 rats (90/sex/dose group) provided diets providing dimethicone (10 cSt, purity not reported) at 0, 100, 300, or 1,000 mg/kg/day for 24 months. An interim sacrifice of 10 animals/sex/group occurred after 12 months of treatment. An additional 20 animals/sex/group were treated for 12 months and then maintained for another 12 months without treatment. The animals were evaluated for clinical signs of toxicity, body weight, food consumption, organ weights, gross pathology, and histopathology. No treatment-related effects were observed on these parameters and the study authors identified a NOAEL of 1,000 mg/kg/day.

- ECETOC 2011, CIR 2022
  - *Dermal:* Dimethicone was administered to three groups of 10 New Zealand White rabbits at 332.5 kg/m-s via occlusive patch for 4 weeks at 0, 100, 300, or 1,000 mg/kg/day. Animals were examined for dermal irritation, body weight, hematology, blood chemistry, and gross and microscopic evaluation of selected organs. There were 29 males and 30 females, but the number/sex/group was not reported. There were no deaths or other treatment-related adverse effects identified. The NOAEL was assigned at 1,000 mg/kg/day, the highest dose tested.

- **Similar Polymer Substance (2b):**
  - Not applicable.
- **Qualifying Constituents (2c):**
  - Not applicable.
- **Professional Judgment (2d):**
  - No relevant information was available.
- Based on the weight of evidence, a score of Low was assigned. The majority of subchronic and chronic studies found no adverse effects following oral exposure to dimethicone. Although one 2-year oral study in male and female Wistar rats found microscopic changes in the lung, ovaries, uterus, liver, and kidney at a dose of 222 mg/kg/day for males or 252 mg/kg/day for females, these values are double the GHS oral guidance value of 100 mg/kg/day. Additionally, as no adverse effects were found in several other studies at much higher doses, the weight of evidence suggests that it is unlikely that adverse effects would be found at doses of 100 mg/kg/day or lower. Furthermore, a 28-day dermal NOAEL of 1,000 mg/kg/day, exceeds the GHS Category 2 guidance value of 200 mg/kg/day for a 90-day study, adjusted to 600 mg/kg/day for a 28-day study (UN 2021).

[30] 50,000 mg/kg * 0.100 kg food/kg BW/day = 5,000 mg/kg/day (males) and 50,000 mg/kg * 0.113 kg food/kg bw/day = 5,650 mg/kg/day. Dose was calculated using the male and female Fisher 344 rat food factor value for a subchronic study (TERA Undated).

Neurotoxicity (N-single) Score (H, M, or L): *L*
Dimethicone was assigned a hazard classification level of Low for single dose neurotoxicity based on lack of clinical signs of toxicity or gross pathological changes in acute oral, dermal, and inhalation studies. GreenScreen® criteria classify polymers as a Low hazard for single dose neurotoxicity when adequate data are available and negative and they are not GHS classified (CPA 2018b, Annex 7). Confidence in the score is low as no specific neurotoxicity endpoints were examined in standard acute toxicity studies.

- **Polymer Substance (2a):**
  - HSDB 2017
    - Dogs (2), guinea pigs (7), and rats (7) were exposed to an aerosol containing an unspecified concentration of dimethicone for 6 hours. Hyperventilation, excitability and salivation were noted during exposure. No additional details were provided.
  - ECETOC 2011
    - *Oral*: In an acute oral toxicity study that identified an oral LD_{50} greater than 4,800 mg/kg in Wistar rats (5/sex) dosed with silicone oil (1,000 cst), no clinical signs of toxicity or gross pathological findings were reported with treatment.
  - ECETOC 2011, CIR 2003
    - *Oral*: In an acute oral toxicity study that identified an oral LD_{50} greater than 2,000 mg/kg in Sprague-Dawley rats (5/sex) dosed with silicone oil (60,000 cst) via gavage, no clinical signs of toxicity or gross pathological findings were reported with a gavage treatment.
  - ECETOC 2011, CIR 2022
    - *Dermal*: In an acute dermal toxicity study that identified a dermal LD_{50} greater than 2,000 mg/kg in New Zealand White rabbits (5/sex) treated with silicone oil (60,000 cSt), no treatment-related gross pathological findings were reported following occlusive application for 24 hours.
    - *Dermal:* Sprague-Dawley rats (5/sex) received dimethicone on the skin at 2,008 mg/kg polydimethylsiloxane according to OECD Test Guideline 402. No behavioral abnormalities were noted during the test period (up to 14 days post dosing) (350cSt).
    - *Inhalation*: In an OECD Guideline 403 acute inhalation toxicity study that identified a 4-hour inhalation LC_{50} greater than 11.582 mg/L in Wistar rats (5/sex), no clinical signs of toxicity were observed during the exposure or observation periods and no gross pathological findings were reported following nose-only exposure to dimethicone dissolved in petroleum ether (100,000 cSt).
    - *Inhalation*: In an OECD Guideline 403 acute inhalation toxicity study that identified a 4-hour inhalation LC_{50} greater than 0.695 mg/L in Wistar rats (5/sex), there were no clinical signs of toxicity during the exposure or observation periods, no changes in reflexes, and no gross pathological findings following exposure to dimethicone dissolved in dichloromethane (10,000 cSt).
- **Similar Polymer Substance (2b):**
  - Not applicable
- **Qualifying Constituents (2c):**
  - Not applicable
- **Professional Judgment (2d):**
  - No relevant information was available.

- Based on the weight of evidence, a score of Low was assigned. Acute oral and dermal studies in rats and/or rabbits found no evidence of behavioral effects, and inhalation studies in rats found no clinical signs of toxicity and/or evidence of changes in reflexes.

Neurotoxicity (N-repeated) (Group II*) Score (H, M, or L): DG
Dimethicone was assigned a hazard classification level of Data Gap for repeated dose neurotoxicity based on a lack of sufficient data. Although no effects on behavior or evidence of neurological effects were reported in subchronic oral studies in rats, it does not appear that any of the studies included a comprehensive neurological battery with assessment of behavior and/or motor activity.

- **Polymer Substance (2a):**
  - ECETOC 2011
    - None of the repeat dose toxicity studies identified reported any adverse neurological effects. It was not clear, however, if neurological endpoints were examined in all the studies. Those that specified some neurological examinations are described again below:
    - *Oral*: In a subchronic oral toxicity study, male rats (100/group, strain not specified) received dimethicone in the diet at 10% (equivalent to 9,600 mg/kg/day[31]) for 90 days. No treatment-related behavioral changes were seen in any group (35, 350 or 1,000 cSt). No additional details, including any on characterization of the test substance, were provided.
    - *Oral:* Fischer 344 rats (50/sex/dose) received KS66 in the diet at doses of 0, 1.25% or 5% (average intakes were 0, 444.9, and 1,893.9 mg/kg/day in females and 0, 530.1 and 2,233.9 mg/kg/day for males) for 104 weeks. No changes were observed on the behavior of the rats (KS66 (a mixture containing 92% dimethicone and 8% silica)). No additional details, including any on characterization of the test substance, were provided.
- **Similar Polymer Substance (2b):**
  - Not applicable.
- **Qualifying Constituents (2c):**
  - Not applicable.
- **Professional Judgment (2d):**
  - No relevant information was available.

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): L
Dimethicone was assigned a hazard classification level of Low for skin sensitization based on negative results in several studies in guinea pigs, mice, and humans. GreenScreen® criteria classify polymers as a Low hazard for skin sensitization when adequate data are available and negative and they are not GHS classified (CPA 2018b, Annex 7). Confidence in the score is high as it is based on consistent measured data in animals and humans.

- **Polymer Substance (2a):**
  - CIR 2003
    - Dimethicone was not sensitizing in guinea pigs. Q7-2167/68 gel (79% dimethicone) (0.1 mL) was applied to the clipped and depilated backs of 10 male Hartley albino guinea pigs under occlusion for 48 hours, 4 times in 10 days. Freund's complete adjuvant (FCA) (0.2 mL) was injected intradermally near the

[31] Average food factor for rats in subchronic studies is 0.096 kg/kg/day (U.S. EPA 1988). 10% in the diet is therefore 10% x 96 g/kg/day = 9.6 g/kg/day = 9,600 mg/kg/day.

test site at the third application. Guinea pigs were challenged at an unexposed site after a 10 day non-treatment period. Reactions were evaluated at 24, 48, and 72 hours post application. No evidence of sensitization was found.

- Dimethicone was not sensitizing in guinea pigs using the Magnusson-Kligman protocol. Dunkin-Hartley guinea pigs (10/sex) received three series of two injections consisting of FCA alone, a 50% (w/w) solution of a trade mixture containing > 90% dimethicone, and FCA plus dimethicone. An SLS patch was applied on day 8 and an occlusive patch containing dimethicone was applied on day 9. Animals were challenged following an 11 day nontreatment period with a 24 hour occlusive patch and challenge sites were evaluated 48 hours after patch removal. No evidence of sensitization was found.
- Dimethicone was not sensitizing in a mouse ear swelling test. Dimethicone fluid (purity not reported) was applied to shaved and abraded skin of female B6C3F1 mice (n=16) for 8 days. Seven days after treatment, mice were challenged on the dorsal and ventral sides of the left ear. Hypersensitivity was measured in half of the treated mice using the radioisotopic incorporation assay. The other half were kept for an additional 7 days, challenged with dimethicone on the left external ear, and hypersensitivity was measured by the mouse ear swelling test. No evidence of a hypersensitivity reaction was found.
- Dimethicone was not sensitizing in guinea pigs when they were tested using a modified split-adjuvant protocol. Q7-2867 (dimethicone liquid, dimethicone purity not reported) (0.2 mL) was applied to the skin of ten male Harley guinea pigs. Four patches were applied under occlusion for 48 hours in 10 days. FCA was injected at the third application and the fourth application occurred 72 hours later. Animals were challenged 12 days later with a 24 hour patch. Challenge sites were evaluated at 24, 48, and 72 hours post application. No evidence of sensitization was found..

- CIR 2022
  - In a human repeat insult patch test (HRIPT), dimethicone (11,875 kg/m*s) was tested neat as a negative control and was used a vehicle for a 5% (v/v) solution of an unspecified test substance. Sodium lauryl sulfate (0.1% aqueous solution) was used as a positive control. 106 subjects were induced with 9 consecutive applications, where 0.2 mL of dimethicone was applied under a semi-occlusive dressing for 24 h. The test sites were evaluated for 48-72 hours, and after the 9th application, there was a 10- to 15-day non-treatment observation period. Then, a challenge occurred on the sixth week of the study where the test substance was applied to an unexposed site for 24 hours and graded after 24-48 hours. No evidence of sensitization to dimethicone as a control or as a vehicle was observed.
- HSDB 2017
  - A solution of 5% (w/v) dimethicone in cyclomethicone was not sensitizing in a repeated insult patch test in 83 Caucasian volunteers. During the induction phase, volunteers were exposed to ten 24 hour patches containing 0.3 mL of the test material. Volunteers were challenged at an unexposed site. The investigators concluded dimethicone is not sensitizing.
- ECETOC 2011
  - A review of guinea pig maximization tests included studies using an induction intradermal dose of 5% v/v to undiluted silicone oil and a challenge dose of undiluted or 75% v/v silicone oil of viscosities ranging from 10 to 60,000 cSt.

No sensitization reactions were observed in these studies and the ECETOC authors concluded that silicone oil is not expected to be sensitizing to human skin.

  - AMA 1980
    - The polydimethylsiloxanes (dimethicone) are not sensitizing to skin.
- **Similar Polymer Substance (2b):**
  - Not applicable.
- **Qualifying Constituents (2c):**
  - Not applicable.
- **Professional Judgment (2d):**
  - No relevant information was available.

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*

Dimethicone was assigned a hazard classification level of Low for respiratory sensitization based on extrapolation from skin sensitization results, and lack of structural alerts and ECHA (2017)'s guidance. GreenScreen® criteria classify polymers as a Low hazard for respiratory sensitization when adequate data are available and negative and they are not GHS classified (CPA 2018b, Annex 7). Confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- **Polymer Substance (2a):**
  - OECD 2023
    - Modeling of dimethicone (representative structure) with OECD QSAR Toolbox identified no structural alerts for respiratory sensitization (Appendix C).
- **Similar Polymer Substance (2b):**
  - Not applicable.
- **Qualifying Constituents (2c):**
  - Not applicable.
- **Professional Judgment (2d):**
  - No respiratory sensitization data were found. However, the guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). As dimethicone was not sensitizing to the skin (see skin sensitization section for details), and a literature search did not find any human evidence of respiratory sensitization, and as it does not contain any structural alerts for respiratory sensitization (OECD 2023), dimethicone is not expected to be a respiratory sensitizer.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M, or L): L

Dimethicone was assigned a hazard classification level of Low for skin irritation/corrosivity based on negative results in several dermal irritation studies in rabbits and a clinical patch test in humans. GreenScreen® criteria classify polymers as a Low hazard for skin irritation/corrosivity when adequate data are available and negative and they are not GHS classified (CPA 2018b, Annex 7). Confidence in the score is high as if is based on negative results in the majority of studies available.

- **Polymer Substance (2a):**
  - HSDB 2017

        - In a clinical study of 54 men, dimethicone (purity not reported) was not irritating to the skin when applied for 24 hours under occlusive conditions. No further details were provided.
    - CIR 2003, 2022
        - Most dermal irritation studies in rabbits found dimethicone to cause minimal dermal irritation. Primary irritation indices of ≤ 2.8 were reported with dimethicone samples ranging from 5% to 100%.
    - CIR 2003
        - Dimethicone (purity not reported) (0.5 mL) applied for 24 hours under occlusive conditions to intact and abraded sites of two rabbits (strain not reported) produced erythema and edema. A maximum score of 8 was reported. A primary irritation index of 6.54 was reported. The authors concluded dimethicone was a severe irritant.
        - No skin irritation was found in eight rabbits following 24 hour treatment with 100% dimethicone on clipped or abraded backs.
        - No skin irritation was found in six New Zealand white rabbits following application of AK 350 (contained an unspecified amount of dimethicone) for 4 hours. Irritation was scored at 1 and 72 hours.
        - In an acute skin irritation study, a trade mixture containing > 90% dimethicone was applied for 4 hours to two sites on six New Zealand White rabbits. At the 1 hour scoring, slight-to-well-defined erythema and very slight edema was observed. Irritation was fully reversible within 72 hours.
    - CIR 2022
        - Three rabbits and 3 guinea pigs were exposed to non-occlusive, daily applications of 0.5 mL of dimethicone (100 cm^2/s) to a 2.5 cm^2 patch of shaved skin for 10 days. No signs of erythema or signs of skin irritation or inflammation were noted in the animals.
    - CIR 2022, ECETOC 2011
        - In an acute dermal toxicity study, undiluted dimethicone (57,000 kg/m*s) was applied to the shaved backs of New Zealand white rabbits (5/sex) under occlusive dressings for 24 hours at a dose of 2,000 mg/kg. Erythema was observed at the application site in all 10 rabbits, but resolved by the 7^{th} day of observation.
    - ECETOC 2011
        - Dermal irritation studies performed with 0.5 mL or 500 mg of silicone oil with viscosities ranging from 20 to 100,000 cSt under semi-occlusive dressings for 4-24 hours did not identify any irritating effects.
        - A review of the available studies indicates that silicone oil can be irritating to the skin under extreme conditions, such as a 24-hour exposure under occlusive dressing. Even under those conditions, the effects were fully reversible. The authors of the ECETOC review concluded that silicone oil is not generally considered to be an irritant to human skin under normal conditions of use.
- **Similar Polymer Substance (2b):**
    - Not applicable.
- **Qualifying Constituents (2c):**
    - Not applicable.
- **Professional Judgment (2d):**
    - No relevant information was available.

- Based on the weight of evidence, a score of Low was assigned. Severe irritation was reported in some animal studies but only under extreme exposure conditions, such as 24 hours under occlusion, and effects were reversible. Studies performed with 4 hours exposure have generally little or no irritation. Humans exposed under extreme conditions of 24 hours under occlusion demonstrated no irritation. Accordingly, the weight of evidence suggests dimethicone is not irritating to the skin of human, and causes little-to-no irritation in animals.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M, or L): *M*
Dimethicone was assigned a hazard classification level of Moderate for eye irritation/corrosivity based on mild ocular irritation in rabbits and ToxServices classifying it as a GHS Category 2B ocular irritant. GreenScreen® criteria classify polymers as a Moderate hazard for eye irritation/corrosivity when a GHS Category 2B classification for ocular irritation is warranted (CPA 2018b, Annex 7). Confidence in the score is low as it is based on limited human data and variable animal data and the lack of sufficient detail to subclassify according to GHS criteria.

- **Polymer Substance (2a):**
  - ECETOC 2011
    - A review of ocular irritation studies indicates that silicone oils over a wide range of viscosities produce no irritation to mild irritation in animals and humans. Low viscosity silicone oil may cause transitory conjunctival redness due to disruption of the tear film, resulting in a "dry eye" effect.
  - CIR 2003
    - Ocular irritation studies in rabbits found mild to moderate ocular irritation.
    - Dow Corning tested three different dimethicone formulations (XF-1-3753, XEF-4-3561, and XF-2-1075) and found no irritation to slight conjunctivitis in rabbits (strain and number not reported). Irritation reversed within 24 hours.
    - Mild irritation was observed in rinsed rabbit (strain and number not reported) following instillation of dimethicone (50% in SM2080). Severe irritation was observed in unrinsed eyes.
    - Mild eye irritation was found following instillation of dimethicone (purity not reported) into the conjunctival sac of three rabbits (strain not reported). A score of 4.7 (max score = 110) was reported)
    - The ocular irritancy of three heat transfer fluids containing dimethicone (% dimethicone not reported) was tested on six rabbits. Two fluids caused no irritation. One fluid produced conjunctival redness in all rabbits and conjunctival chemosis in two rabbits. Chemosis and redness were fully reversible within 48 hours and 7 days, respectively.
    - Slight irritation was observed following instillation of a trade mixture containing dimethicone (% dimethicone not reported) into one eye of six rabbits (strain not reported).
    - No irritation was observed following instillation of 0.1 mL of a trade mixture containing > 90% dimethicone into one eye of six rabbits (strain not reported).
  - HSDB 2017, CIR 2003
    - Rabbits tested with 0.005, 0.01, and 0.1 mL doses of a mixture containing 15% dimethicone had mild to moderate conjunctival irritation (0.005 mL), moderate conjunctival irritation and moderate iritis (0.01 mL), and moderate corneal injury, iritis, and conjunctival irritation (0.1mL).

        - Dimethicone at 10% and 29% produced no irritation, but slight conjunctivitis or iritis was noted at 35%; irritation cleared within 24 hours. No further details were provided.
    - HSDB 2002
        - The lower viscosity oils cause slight transient sensation of irritation when applied to human eyes, but no injury of the cornea.
- **Similar Polymer Substance (2b):**
    - Not applicable.
- **Qualifying Constituents (2c):**
    - Not applicable.
- **Professional Judgment (2d):**
    - No relevant information was available.
- Based on the weight of evidence, a score of Moderate was assigned. Studies in rabbits found no to moderate ocular irritation following instillation of dimethicone; however, limited study details were provided and irritation scores were not reported. Based on mild irritation reported in animal studies that appears to be reversible, dimethicone was classified as GHS Category 2B and a score of Moderate was assigned.

ECOTOXICITY (ECOTOX)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): L
Dimethicone was assigned a hazard classification level of Low for acute aquatic toxicity based on LC_{50} values several orders of magnitude higher than the water solubility indicating a lack of effects at saturation. GreenScreen® criteria classify polymers as a Low hazard for acute aquatic toxicity when there are no effects at saturation (CPA 2018b, Annex 7). Confidence in the score is high as it is based on experimental water solubility and reliable measured data.

- **Polymer Substance (2a):**
    - Nendza 2007
        - The soluble fractions of silicone oil have low toxicity to aquatic and benthic organisms.
    - U.S. EPA 2023
        - 96-hour LC_{50} (*Lepomis microlophus*, redear sunfish) = 37.790 mg/L
        - 96-hour LC_{50} (*Ictalurus punctatus*, channel catfish) = 3.16 mg/L
        - 48-hour LC_{50} (*Daphnia magna*) = 44.5 mg/L
            - The database does not specify if these are measured or nominal values. However, as the water solubility of dimethicone is very low, ToxServices assumes that they are nominal values.
    - ECETOC 2011
        - Silicone oil has a predicted water solubility of less than 1 ng/L.
        - 48-hour LC_{50} (*D. magna*) = greater than 0.1 mg/L (water accommodated fraction)
        - In *Mytilus edults* (mussels) exposed to dimethicone (50 cSt) emulsion for 96 hours, the LC_{50} was >1,020 mg/kg d.w.
        - In *Mytilus edults* (mussels) exposed to dimethicone (50 cSt) 20% emulsion for 96 hours, the LC_{50} was 1,980 mg/kg d.w.
        - The 10-hour EC_{50} in *Corophium volutator* (marine amphipods) exposed to dimethicone (10 cSt) was >30,715 mg/kg.
        - The 10-hour EC_{50} in *Corophium volutator* (marine amphipods) exposed to dimethicone (350 cSt) was >1,523 mg/kg.

        - 72-hour growth rate and biomass EC_{50} (*Skeletonema costatum*, diatom) > 100,000 mg/L (nominal)
        - Polydimethylsiloxane has no effects when tested on aquatic organisms (fish, daphnia, algae).
- **Similar Polymer Substance (2b):**
    - Not applicable.
- **Qualifying Constituents (2c):**
    - Not applicable.
- **Professional Judgment (2d):**
    - No relevant information was available.
- Based on the weight of evidence, a score of Low was assigned. Although some values in fish and daphnia are less than the guidance value for classification, dimethicone is highly insoluble (< 1 ng/L). As all acute aquatic toxicity values are above the limit of solubility for polydimethylsiloxanes, no acute aquatic toxicity is expected at saturation.

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *L*

Dimethicone was assigned a hazard classification level of Low for chronic aquatic toxicity based on data indicating no effects at saturation. GreenScreen® criteria classify polymers as a Low hazard for chronic aquatic toxicity when there are no effects at saturation (CPA 2018b, Annex 7). Confidence in the score is low as there are insufficient data available for fish and no standard aquatic toxicity data available for daphnia.

- **Polymer Substance (2a):**
    - HSDB 2017
        - Dimethicone is not soluble in water.
    - ECETOC 2011
        - Silicone oil has a predicted water solubility of less than 1 ng/L.
        - A fish early life-stage test was conducted with sheepshead minnow (*Cyprinodon variegatus*) embryos exposed to a dimethicone (50 cSt) emulsion for 33 days. Adverse effects on hatchability were observed at 606 mg emulsion/L, equivalent to 212 mg dimethicone/L. The control emulsion without dimethicone caused significant mortality and reduction in larval weight and length compared to the blank control. Authors concluded the adverse effects were partially due to the emulsion components.
            - ToxServices notes these study details are insufficient to derive a NOEC.
        - *Oncorhynchus mykiss* (rainbow trout) were exposed to dimethicone (350 cSt) for 28 days in the feed, equivalent to 10 mg dimethicone/day, or 10,000 mg/kg-bw, followed by a 14-day recovery period. There were no mortalities or changes in behavior or growth in treated fish compared to controls. Histopathological examination of skin, muscle, liver, bile, adrenal, stomach, and gut, revealed no abnormalities. While no toxicity was observed, authors state it was a non-standard toxicity study and a meaningful NOEC cannot be derived.
        - 21-day reproduction NOEC (*D. magna*) = 572 mg/kg sediment (sediment treated with ^{14}C-labeled material)
        - 72-hour growth rate and biomass EC_{50} (*S. costatum*, diatom) = 33,900 mg/L (nominal)
            - No ^{14}C was measured in the overlying water, consistent with the limited water solubility of silicone oil.

        - The 20-day NOEC in *Chironomus tentans* (midge larva) exposed to dimethicone (350 cSt) was > 2,590 mg/kg d.w. (EPA/600/R-99/064).
        - The 14-day NOEC in *Chironomus tentans* (midge) exposed to dimethicone (350 cSt) was > 560 mg/kg d.w. (EPA/600/R-99/064).
        - The 28-day NOEC in *Hyallela azteca* (freshwater amphipod) exposed to dimethicone was > 2,200 mg/kg d.w. (EPA/600/R-99/064).
        - The 42-day NOEC in *Hyallela azteca* (freshwater amphipod) exposed to dimethicone was > 994 mg/kg d.w. (EPA/600/R-99/064).
- **Similar Polymer Substance (2b):**
    - Not applicable.
- **Qualifying Constituents (2c):**
    - Not applicable.
- **Professional Judgment (2d):**
    - No relevant information was available.
- Based on the weight of evidence, a score of Low was assigned. As discussed previously, dimethicone has very low water solubility, which is demonstrated by a lack of effects in a sediment study with daphnia and an EC_{10} of greater than 33,900 mg/L in algae. Although insufficient fish data and no standard aquatic daphnia data were identified, the available data, in conjunction with the very low water solubility, indicate no effects at saturation.

ENVIRONMENTAL FATE (FATE)

Persistence (P) Score (vH, H, M, L, or vL): *vH*
Dimethicone was assigned a hazard classification level of Very High for persistence based on the weight of evidence indicating that it is expected to be persistent in the environment. GreenScreen® criteria classify polymers as a Very High hazard for persistence when they are recalcitrant or have half-lives greater than 180 days in soil or sediment and 60 days in water (CPA 2018b, Annex 7). Confidence in the score is low due to limited data and as it is based on expert judgement.

- **Polymer Substance (2a):**
    - Danish Ministry of the Environment 2005
        - Siloxanes are stable compounds and are very persistent in the environment.
    - Cragg 2001
        - Radioactive tracer studies of ^{14}C-polydimethylsiloxane showed no detectable degradation by sewage microorganisms.
    - Nendza 2007
        - Silicone oils are generally considered highly persistence. They have on BOD in biodegradation tests, show less than 10% degradation in 6 months, and have hydrolysis half-lives ranging from months to years.
    - ECETOC 2011
        - Polydimethylsiloxanes break down slowly via abiotic processes when in contact with soil.
        - As dimethicone is non-volatile, vapors are not expected to be found in the atmosphere. Due to low solubility of dimethicone in water, if discharged as effluent, it is less dense than water and will partition to the surface layer and likely adsorb to particular matter.
        - Hydrolysis is expected to be slow based on measured data. After an incubation period of 1 year in sediment, 5-10% of ^{14}C-polydimethylsiloxane hydrolyzed to

dimethylsilanediol (DMSD), and approximately 0.25% oxidized to carbon dioxide.
    - U.S. EPA 2013
        - The vast majority of polymers are essentially non-biodegradable.
- **Similar Polymer Substance (2b):**
    - Not applicable.
- **Qualifying Constituents (2c):**
    - Not applicable. There are no qualifying constituents for this endpoint.
- **Professional Judgment (2d):**
    - No relevant information was available.
- Based on the weight of evidence, a score of Very High was assigned. Limited data were identified for dimethicone, and included only descriptions of slow degradation in soil and hydrolysis, with less than 10% degradation in 10 months. As dimethicone is a polymer, modeling using EPI Suite™ was not performed. Dimethicone is associated with the EC – CEPA DSL – Persistent screening list (Pharos 2023) which warrants a High to Very High score. The Danish Ministry of the Environment (2005) indicated that siloxanes are stable compounds that are very persistent in the environment. Therefore, a score of Very High was assigned.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *vL*
Dimethicone was assigned a hazard classification level of Very Low for bioaccumulation based on lack of bioavailability due to very high molecular weight (i.e., >1,000) and expert judgement by U.S. EPA and others, as large, non-ionic polymers with low water solubility and high log K_{ow} typically do not bioaccumulate. GreenScreen® criteria classify polymers as a Very Low hazard for bioaccumulation when the BCF is no greater than 100 (CPA 2018b, Annex 7). Confidence in the score is low as it is based in part on expert judgment.

- **Polymer Substance (2a):**
    - Danish Ministry of the Environment 2005
        - No measured bioaccumulation data were identified; therefore, the U.S. EPA's PBT profiler was used to predict the bioaccumulation potential of two linear methyl siloxanes (hexamethyldisiloxane, CAS# 107-46-0 and octamethyltrisiloxane, CAS# 107-51-7). The U.S. EPA PBT profiler predicted log K_{ow} values of 4.2 and 4.8 and BCF values of 340 and 990 for hexamethyldisiloxane and octamethyltrisiloxane, respectively.
    - U.S. EPA 2013
        - Due to the large size and insolubility of most polymers, they are typically of low concern for bioconcentration.
    - Cragg 2001
        - Radioactive tracer studies with ^{14}C-polydimethylsiloxane showed no bioaccumulation in bluegill sunfish.
        - Silicon residues in eggs and tissue samples of white Leghorn chickens were below the detection limit of 2 to 4 ppm after the chickens had been maintained on diets that contained 200 to 5,000 ppm polydimethylsiloxane.
    - ECETOC 2011
        - Based on the low water solubility, high log K_{ow} (at least 8.21), large molecular size, and high affinity for organic matter, dimethicone is not likely to bioaccumulate in tissues.
    - Environment Canada 2011, ECETOC 2011

        - Only one study reported that dimethicone may have high bioaccumulation potentials, for which limited details were provided for examination. Measured data from other studies in aquatic, soil and sediment organisms on dimethicone with a variety of molecular weights (MW=1,200 g/mol and above) revealed that these compounds are not expected to be bioavailable and hence unlikely to have any bioaccumulation potential.
        - Bioconcentration studies on dimethicone with short chain (up to 12) indicate that the potential for dimethicone fluids with viscosity > 10 cSt to cross the biological membranes is very unlikely due to their molecular size.
    - Sigma-Aldrich 2023
        - Average molecular weight for polydimethylsiloxane is 95,000 g/mol.
- **Similar Polymer Substance (2b):**
    - Not applicable.
- **Qualifying Constituents (2c):**
    - Not applicable. There are no qualifying constituents for this endpoint.
- **Professional Judgment (2d):**
    - No relevant information was available.
- Based on the weight of evidence, a score of Very Low was assigned. As dimethicone is a polymer, modeling using EPI Suite™ was not performed. A safety data sheet for dimethicone indicates it has a log K_{ow} between 2.6 and 4.25, which corresponds to a Very Low to Moderate score. This is consistent with log K_{ow} values predicted for two other linear methyl siloxanes. However, these lower molecular weight species are not representative of the high molecular weight nature of dimethicone. Dimethicone has viscosities of 100 – 1,500 cSt (FAO 2008), which is greater than 10 cSt that is considered to have low bioaccumulation potential by European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). Measured data in aquatic, soil and sediment organisms on dimethicone with a variety of molecular weights (MW=1,200 g/mol and above) indicate that these compounds are unlikely to have any bioaccumulation potential supporting a score of Very Low.

PHYSICAL HAZARDS (PHYSICAL)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Dimethicone was assigned a hazard classification level of Low for reactivity based on an NFPA rating of 0 for reactivity. GreenScreen® criteria classify polymers as a Low hazard for reactivity when they adequate data are available and negative and they are not GHS classified for any of the reactivity sub-endpoints (CPA 2018b, Annex 7). Confidence in the score is low due to the lack of experimental data.

- **Polymer Substance (2a):**
    - Fischer Science 2020
        - A safety data sheet for a product containing 100% polydimethylsiloxane indicates that it has a instability hazard rating of 0 from NFPA ("Normally stable, even under fire exposure conditions, and are not reactive with water") (ILPI 2023).
- **Similar Polymer Substance (2b):**
    - Not applicable.
- **Qualifying Constituents (2c):**
    - Not applicable. There are no qualifying constituents for this endpoint.
- **Professional Judgment (2d):**
    - No relevant information was available.

Flammability (F) Score (vH, H, M, or L): L

Dimethicone was assigned a hazard classification level of Low for flammability based on ToxServices not classifying it under GHS based on measured flash points of ≥316°C. GreenScreen® criteria classify polymers as a Low hazard for flammability when they are not classified for flammability under GHS (CPA 2018b, Annex 7). Confidence in the score is high as it is based on an experimental flash point.

- **Polymer Substance (2a):**
  - Fisher Science 2020
    - Silicone oil has a flash point of 341°C (645.8°F) (ISO 2592). No additional details were reported.
  - Sigma-Aldrich 2023
    - Silicone oil has a flash point of 316.00°C (600.8°F) (Closed Cup Test). No additional details were reported.
- **Similar Polymer Substance (2b):**
  - Not applicable.
- **Qualifying Constituents (2c):**
  - Not applicable. There are no qualifying constituents for this endpoint.
- **Professional Judgment (2d):**
  - No relevant information was available.
- Based on the weight of evidence, a score of Low was assigned. The flash point exceeds the threshold of 93ºC for GHS classification (UN 2021).

USE OF NEW APPROACH METHODOLOGIES (NAMS)[32] IN THE ASSESSMENT, INCLUDING UNCERTAINTY ANALYSES OF INPUT AND OUTPUT

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for respiratory sensitization; use of *in vitro* data for mutagenicity and endocrine activity; and reliance on physicochemical properties to assess bioaccumulation. NAMs are non-animal alternatives that can be used alone or in combination to provide information for safety assessment (Madden et al. 2020). At present, there is not a uniformly accepted framework on how to report and apply individual NAMs (U.S. EPA 2020, OECD 2020). The expanded application of NAMs greatly amplifies the need to communicate uncertainties associated with their use. As defined by EFSA (2018), uncertainty is "a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question." The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties (OECD 2020):

- Type I: Uncertainties related to the input data used
- Type II: Uncertainties related to extrapolations made

As shown in Table 6, Type I (input data) uncertainties in dimethicone's NAMs dataset include lack of sufficient *in vivo* data for all critical endocrine pathways, lack experimental data and no validated test methods for respiratory sensitization, and no experimental data for bioaccumulation. Dimethicone's Type II (extrapolation output) uncertainties include reliance on structural alerts for the respiratory sensitization endpoint where the applicability domain is not defined; uncertain relevance of *in vitro* endocrine data for the qualifying constituents; reliance on *in vitro* data for genotoxicity and endocrine activity that captures key events but may not account for all events in an adverse outcome pathway and/or may not account for *in vivo* metabolism, lack of consideration of non-immunologic mechanisms for respiratory sensitization during the assessment of structural alerts, and uncertainty in the bioaccumulation of oligomers when evaluation is solely based on physicochemical properties of the polymers. Some of dimethicone's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 6: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Endocrine activity:** Insufficient *in vivo* data are available for all critical endocrine pathways. **Respiratory sensitization**: No experimental data are available and there are no validated test methods for this endpoint. **Bioaccumulation:** No experimental data are available.
Type II Uncertainty: Extrapolation Output	**Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[33]. The

[32] NAMs refers to any non-animal technology, methodology, approach, or combination thereof that inform chemical hazard and risk assessments. NAMs include *in silico*/computational tools, *in vitro* biological profiling (e.g., cell cultures, 2,3-D organotypic culture systems, genomics/transcriptomics, organs on a chip), and frameworks (i.e., adverse outcome pathways (AOPs), defined approaches (DA), integrated approaches to testing and assessment (IATA).

[33] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427

	mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[34] The *in vitro* chromosome aberration assay (OECD Guideline 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[35]. The cell transformation assay, a test method for carcinogenicity, has a number of limitations, including the subjectivity in judging transformed phenotypic morphology, the limited understanding of the molecular mechanisms leading to transformation, and the small number of non-genotoxic carcinogens used to establish this assay[36]. **Endocrine activity:** *In vitro* data of qualifying constituents may not be relevant to the toxicity of the polymer. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization. **Bioaccumulation:** Analysis of bioaccumulation based on average molecular weight does not account for low molecular weight fractions and/or impurities.

Endpoint	NAMs Data Available and Evaluated? (Y/N)	Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)
Carcinogenicity	N	
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay / *in vitro* gene mutation assay / *in vitro* chromosome aberration assay / *in vitro* mammalian cell transformation assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In vitro* data
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	

[34] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[35] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352
[36] https://www.oecd.org/env/ehs/testing/Guidance-Document-on-the-in-vitro-Syrian-Hamster-Embryo-Cell-Transformation-Assay.pdf

Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	N	
Bioaccumulation	Y	Assessed based on physicochemical properties

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APPENDIX A: HAZARD BENCHMARK ACRONYMS (alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: RESULTS OF AUTOMATED GREENSCREEN® SCORE CALCULATION FOR DIMETHICONE (CAS #63148-62-9/9006-65-9/9016-00-6)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	Chemical Name	CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No	Dimethicone	63148-62-9	L	L	*L*	L	DG	L	L	L	*L*	DG	L	*L*	L	*M*	L	*L*	*vH*	*vL*	*L*	L

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	No		
2	No	No	Yes	No	No	No	No
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Dimethicone	2

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

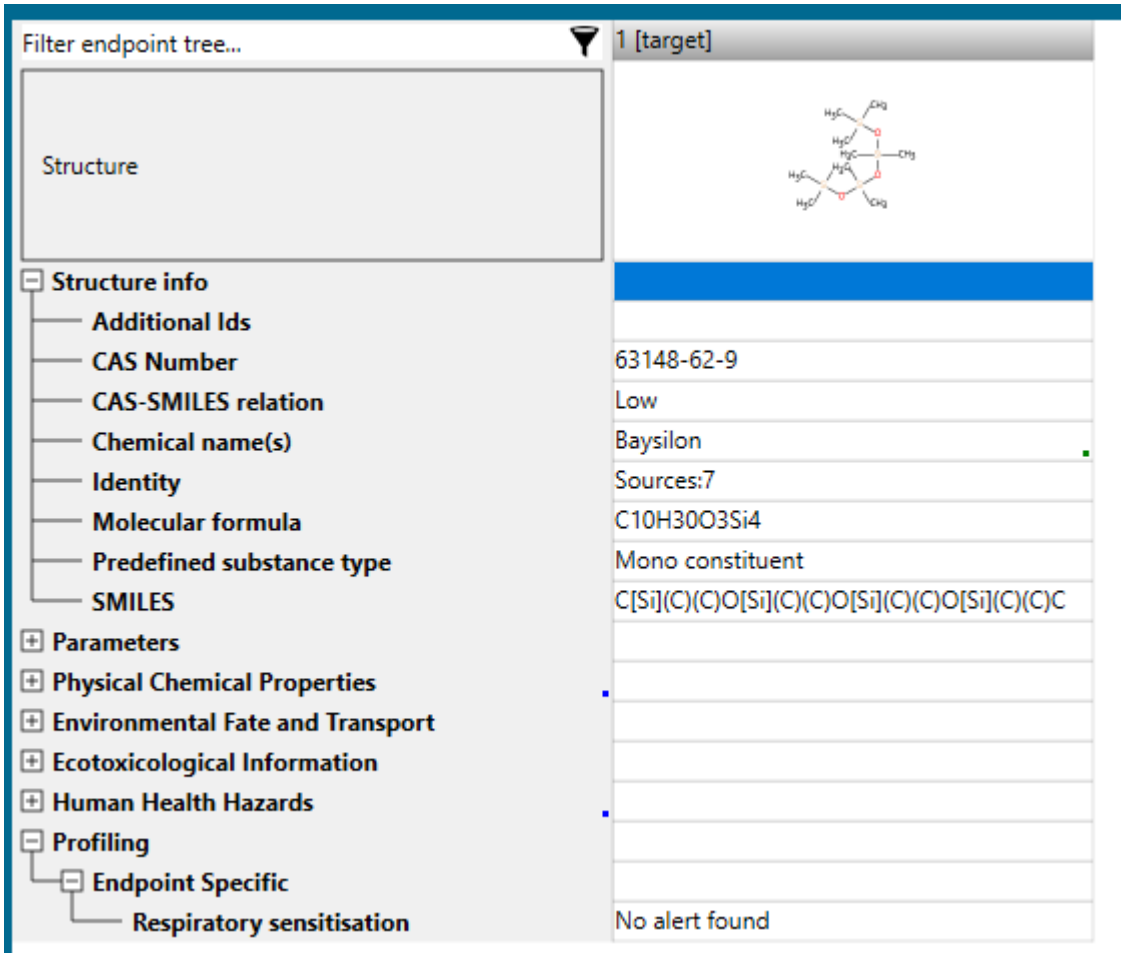
Chemical Name	Final GreenScreen® Benchmark Score
Dimethicone	2

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2	Yes	Yes	Yes	Yes	Yes							2
3												
4												

APPENDIX C: OECD TOOLBOX RESPIRATORY SENSITIZATION MODELING FOR DIMETHICONE (CAS #63148-62-9/9006-65-9/9016-00-6)



APPENDIX D: CHANGE IN BENCHMARK SCORE

Table 7 provides a summary of changes to ToxServices' GreenScreen® Benchmark™ for dimethicone. ToxServices performed the original GreenScreen® assessment in 2019 under version 1.4 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score is maintained with the current version 1.4 update.

Table 7: Change in GreenScreen® Benchmark™ for Dimethicone

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
September 4, 2019	BM-2	v. 1.4	Original GreenScreen® assessment.
August 28, 2023	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with a v.1.4 template.

LICENSED GREENSCREEN® PROFILERS

Dimethicone GreenScreen® Evaluation Prepared by:

SIGNATURE BLOCK

Jennifer Rutkiewicz, Ph.D.
Senior Toxicologist
ToxServices LLC

Dimethicone GreenScreen® Evaluation Updated by:

SIGNATURE BLOCK

Rachel Doerer, M.P.H.
Toxicologist
ToxServices LLC

Dimethicone GreenScreen® Evaluation QC'd by:

SIGNATURE BLOCK

Bingxuan Wang, Ph.D., D.A.B.T.
Senior Toxicologist
ToxServices LLC