Draft Screening Assessment

Siloxanes Group

Chemical Abstracts Service Registry Numbers
107-46-0
141-62-8
141-63-9
541-05-9
2627-95-4
69430-24-6

Environment and Climate Change Canada
Health Canada

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Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment on six of seven substances referred to collectively under the Chemicals Management Plan as the Siloxanes Group. These six substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA. One of the seven substances was subsequently determined to be of low concern for risk to both the environment and human health and the decision for this substance is provided in a separate report.[1] Accordingly, this screening assessment addresses the six substances listed in the table below, hereinafter referred to as the Siloxanes Group.

Substances in the Siloxanes Group

CAS RN[a]	*Domestic Substances List* name	Common name (abbreviation)
107-46-0	Disiloxane, hexamethyl-	Hexamethyldisiloxane (L2)
141-62-8	Tetrasiloxane, decamethyl-	Decamethyltetrasiloxane (L4)
141-63-9	Pentasiloxane, dodecamethyl-	Dodecamethylpentasiloxane (L5)
541-05-9	Cyclotrisiloxane, hexamethyl-	Cyclotrisiloxane (D3)
2627-95-4	Disiloxane, 1,3-diethenyl-1,1,3,3-tetramethyl-	Divinyltetramethyldisiloxane (dvTMDS)
69430-24-6[b]	Cyclosiloxanes, di-Me	Cyclomethicone

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[b] This substance is a UVCB (unknown or variable composition, complex reaction products, or biological materials).

The substances in the Siloxanes Group do not naturally occur in the environment. According to the information submitted in response to a survey under section 71 of CEPA, 1 000 to 100 000 kg for each of L2, L4, L5, D3 and dvTMDS was reported to be imported into Canada in 2008. In the same year, no Canadian manufacturing activity was reported for these five substances above the reporting threshold of 100 kg. Although cyclomethicone was not reported to be manufactured or imported above the reporting threshold of 100 kg in 2011, it is an ingredient in products available to consumers.

In Canada, L2, L4, L5 and D3 are primarily used as intermediates, solvents, skin conditioning agents, surface active agents, polymers and functional fluids in products

[1] The conclusion for CAS RN 33204-76-1 is provided in the Rapid Screening of Substances with Limited General Population Exposure Screening Assessment.

available to consumers such as cosmetics, natural health products, electronics, medical devices, adhesives and sealants, as well as in industrial applications such as paints and coatings. L2 and dvTMDS are used as intermediates in the manufacture of polymers and other organic compounds. L5 is in sunscreens available to Canadian consumers and dvTMDS may be used in food packaging materials. Cyclomethicone is used in various products including cosmetics.

The ecological risks of the substances in the Siloxanes Group were characterized using the ecological risk classification of organic substances (ERC), which is a risk-based approach that employs multiple metrics for both hazard and exposure based on weighted consideration of multiple lines of evidence for determining the risk classification. Hazard profiles are established based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Metrics considered in the exposure profiles include potential emission rate, overall persistence, and long-range transport potential. A risk matrix is used to assign a low, moderate or high level of potential concern for substances based on their hazard and exposure profiles. Based on the outcome of the ERC analysis, the substances in the Siloxanes Group are considered unlikely to be causing ecological harm.

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from substances in the Siloxanes Group. It is proposed to conclude that L2, L4, L5, D3, dvTMDS and cyclomethicone in the Siloxanes Group do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

For the human health risk assessment, the linear siloxanes (L2, L4 and L5) were considered as a subgroup; D3 and dvTMDS were considered as individual substances; and cyclomethicone is a UVCB. For the general population of Canada, indoor air is the predominant source of exposure from environmental media to the linear siloxanes subgroup and D3. Oral exposure to D3 may occur from eating fish. Exposure to dvTMDS via environmental media or food packaging materials is considered to be negligible. From the use of products available to consumers, the predominant sources of exposure to the linear siloxanes subgroup and D3 are from use of cosmetics that contain these substances (such as L2 in nail polish drying drops and bandage adhesive remover, L4 in lip balms and D3 in face cream), and from use of sunscreens containing L5. Exposure of the general population to dvTMDS from use of products available to consumers is not expected.

Cyclomethicone is primarily comprised of three substances previously assessed under CEPA (D4, D5 and D6). For each of these three primary components (D4, D5 and D6), margins of exposure are considered to be adequate to address uncertainties in the health effects and exposure databases. Accordingly, human exposures and human

health effects associated with cyclomethicone are not further characterized in this assessment.

In laboratory studies, L2 affects the liver, testes, and lungs, whereas L4 affects the liver. L5 may have similar effects, on the basis of a read-across approach used to characterize its critical health effects. D3 resulted in effects including decreased food consumption, body weight, and liver weight. DvTMDS was not identified as posing a high hazard to human health on the basis of classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

For L2, L4, L5, D3 and dvTMDS, estimates of exposure were derived based on levels of substances in environmental media including indoor air as the largest contributor for exposure, and products available to consumers, such as cosmetics. On the basis of these estimates of exposure compared with critical effect levels identified from studies in experimental animals, margins of exposure are considered to be adequate to address uncertainties in the health effects and exposure databases.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that L2, L4, L5, D3, dvTMDS and cyclomethicone do not meet the criteria under paragraph 64(*c*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is proposed to conclude that L2, L4, L5, D3, dvTMDS and cyclomethicone do not meet any of the criteria set out in section 64 of CEPA.

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1. Introduction

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have conducted a screening assessment on six of seven substances referred to collectively under the Chemicals Management Plan (CMP) as the Siloxanes Group to determine whether these substances present or may present a risk to the environment or to human health. The six substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA (ECCC, HC [modified 2017]).

The other substance (CAS RNs[2] 33204-76-1, cyclotetrasiloxane, 2,2,4,6,6,8-hexamethyl-4,8-diphenyl-, cis-) was considered in the Ecological Risk Classification of Organic Substances (ERC) Science Approach Document (ECCC 2016a) and via the approach applied in the Rapid Screening of Substances with Limited General Population Exposure (ECCC, HC 2018a) and was identified as being of low concern to both human health and the environment. As such, it is not further addressed in this report. Conclusions for this substance are provided in the Rapid Screening of Substances with Limited General Population Exposure Screening Assessment Report (ECCC, HC 2018a).

The ecological risks of the six substances in the Siloxanes Group addressed in this document were characterized using the ERC approach (ECCC 2016a). The ERC describes the hazard of a substance using key metrics including mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity and considers the possible exposure of organisms in the aquatic and terrestrial environments based on factors including potential emission rates, overall persistence and long-range transport potential in air. The various lines of evidence are combined to identify substances as warranting further evaluation of their potential to cause harm to the environment or as having a low likelihood of causing harm to the environment.

For the assessment of human health risk of the six substances addressed in this document, empirical data from key studies as well as results from models were used to reach proposed conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

Cyclomethicone (CAS RN 69430-24-6) is a mixture of low molecular weight volatile cyclic siloxanes, the principal ingredients of which are octamethylcyclotetrasiloxane (D4), decamethylcyclopentasiloxane (D5) and dodecamethylcyclohexasiloxane (D6), in

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varying proportions (Environment Canada, Health Canada 2008a, 2008b, 2008c). The exposure and human health effects of cyclomethicone have been assessed as part of the D4, D5, and D6 assessments (Environment Canada, Health Canada 2008a, 2008b, 2008c), and those assessments form the basis of the proposed conclusions for cyclomethicone in this assessment.

Three substances in the Siloxanes Group (L2, L4, and L5), are also components of dimethicone (CAS RN 9006-65-9). Dimethicone is a mixture of fully methylated linear siloxane polymers end-blocked with trimethylsiloxy units (CIR 2003). The exposure and human health effects of dimethicone as a mixture was previously assessed in the second phase of polymer rapid screening of the CMP (ECCC, HC 2018b) and is not further addressed in this document. Only the exposure potential and human health effects of L2, L4, and L5 as individual substances are considered in this assessment.

Three substances (L2, D3, dvTDMS) in the Siloxanes Group have been reviewed internationally through the OECD Cooperative Chemicals Assessment Programme and there are existing assessments available. These assessments undergo rigorous review (including peer-review) and endorsement by international governmental authorities. Health Canada and Environment and Climate Change Canada are active participants in this process, and consider these assessments to be reliable. The OECD assessments on L2, D3 and dvTDMS (OECD 2009, 2013, 2014) informed the health effects characterizations in this screening assessment.

This draft screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposures, including additional information submitted by stakeholders. Relevant data were identified up to December 2017. However, a limited number of more recent studies or information provided via internal and external peer consultation may also be cited.

This draft screening assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The human health portions of this assessment have undergone external review and/or consultation. Comments on the technical portions relevant to human health were received from Herman Gibb, Joan Garey, Theresa Lopez and Jennifer Flippin of Tetra Tech. The ecological portion of this assessment is based on the ERC document (published July 30, 2016), which was subject to an external review as well as a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

This draft screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by examining scientific

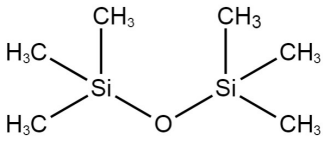
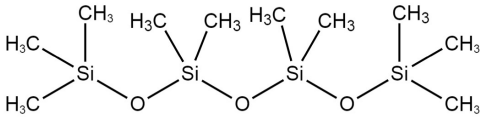
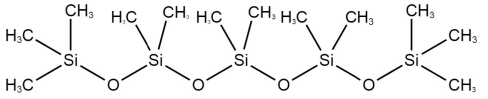
information and incorporating a weight of evidence approach and precaution.[3] This draft screening assessment presents the critical information and considerations on which the proposed conclusions are based.

2. Identity of substances

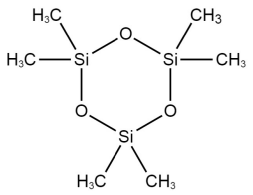
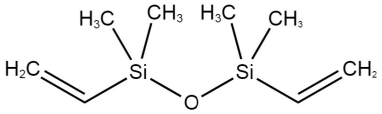
The CAS RNs, abbreviations, and *Domestic Substances List* (DSL) names for the individual substances in the Siloxanes Group are presented in Table 2-1.

For the purposes of this screening assessment, the six substances discussed are divided into the linear siloxanes subgroup (L2, L4, and L5) and three individual substances based on their chemical structure, properties and/or toxicity.

Table 2-1. Substance identities of the Siloxanes Group

CAS RN (abbreviation)	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
107-46-0 (L2)	Disiloxane, hexamethyl- (hexamethyldisiloxane)	 $C_6H_{18}OSi_2$	162.38
141-62-8 (L4)	Tetrasiloxane, decamethyl- (decamethyltetrasiloxane)	 $C_{10}H_{30}O_3Si_4$	310.69
141-63-9 (L5)	Pentasiloxane, dodecamethyl- (dodecamethylpentasiloxane)	 $C_{12}H_{36}O_4Si_5$	384.84

[3]A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products available to consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Hazardous Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other acts.

CAS RN (abbreviation)	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
541-05-9 (D3)	Cyclotrisiloxane, hexamethyl- (cyclotrisiloxane)	 $C_6H_{18}O_3Si_3$	222.46
2627-95-4 (dvTMDS)	Disiloxane, 1,3-diethenyl-1,1,3,3-tetramethyl- (divinyltetramethyldisiloxane)	 $C_8H_{18}OSi_2$	186.40
69430-24-6	Cyclosiloxanes, di-Me (Cyclomethicone)[a]	UVCB	N/A

Abbreviations: N/A, not applicable.

[a] Cyclomethicone is a mixture of low molecular weight volatile cyclic siloxanes, the principal ingredients of which are octamethylcyclotetrasiloxane (D4), decamethylcyclopentasiloxane (D5) and dodecamethylcyclohexasiloxane (D6), in varying proportions.

2.1 Selection of Analogues

A read-across approach using data from analogues and the results of (quantitative) structure-activity relationship ((Q)SAR) models, where appropriate, has been used to inform the ecological and human health assessments. Analogues were selected that were structurally and/or functionally similar to substances within this group (similar physical-chemical properties, toxicokinetics), and that had relevant empirical data that could be used to read-across to substances with limited empirical data.

In the linear siloxanes subgroup for the human health effects assessment, data from one or more substances were used to inform other substances within this subgroup (Appendix D. Hazard summary and read across within the linear siloxanes subgroup). In most cases, L2 was used for read-across to selected critical health effects for L4 and L5.

3. Physical and chemical properties

A summary of physical and chemical property data for the substances in the Siloxanes group are presented in Table 3-1. Additional physical and chemical properties are presented in ECCC (2016b). Physical and chemical properties of cyclomethicone, a mixture of low molecular weight volatile cyclic siloxanes, can vary depending on the proportion of its constituents in the mixture, and thus are not provided in this table. Physical and chemical properties of its main components, D4, D5 and D6, can be found

in the published Screening Assessment for D4, D5 and D6 (Environment Canada, Health Canada 2008a, 2008b, 2008c).

Table 3-1. Physical and chemical property values (at standard temperature) for the Siloxanes Group[a]

Property	L2	L4	L5	D3	dvTMDS
Physical state	liquid	liquid	liquid	solid	liquid
Melting point (°C)	-68.2	-73	-80	64	-99.7
Vapour pressure (Pa at 25°C)	4 451 (at 20°C)	73	7.8	1156	1 655
Henry's law constant ($Pa \cdot m^3/mol$)	5.1×10^5	2.59×10^6	2.0×10^7	6 484 [modelled][b]	1.49×10^6 [modelled]
Water solubility (mg/L)	9.3×10^{-1}	6.74×10^{-3}	7.04×10^{-5}	1.6	0.207
Log K_{ow} (dimensionless)	5.2	8.21	9.41	4.38 [modelled]	5.36
Log K_{oc} (dimensionless)	2.53	5.16	6.3	N/A	N/A

Abbreviations: K_{ow}, octanol–water partition coefficient; K_{oc}, organic carbon–water partition coefficient; N/A, not applicable.

[a] OECD (2013) and ECHA (2017b, 2017c, 2017d) for the linear siloxanes, OECD (2009) for D3, and OECD (2014) for dvTMDS unless otherwise stated. Experimental values unless otherwise indicated.

[b] ChemIDplus (1993-)

4. Sources and uses

None of the six substances in the Siloxanes Group naturally occur in the environment (Rücker and Kummerer 2015).

L2, L4, L5, D3, and dvTMDS in the Siloxanes Group have been surveyed in 2009 pursuant to a CEPA section 71 of CEPA notice (Environment Canada 2009). Table 4-1 presents a summary of the reported total manufacture and total import quantities for the six substances in the Siloxanes Group.

Table 4-1. Summary of information on Canadian manufacturing and imports of L2, L4, L5, D3, and dvTMDS submitted pursuant to a CEPA section 71 survey

Common name	Total manufacture[a] (kg)	Total Imports[a] (kg)
L2	< 100	15 500 - 80 000
L4	NR	29 200 – 92 000
L5	NR	13 200 - 57 000
D3	NR	1 000 - 100 000
dvTMDS	NR	1 000 - 100 000
Cyclomethicone	NR	NR

Abbreviations: NR, not reported above the reporting threshold of 100 kg (Environment Canada 2009).

[a] Values reflect quantities reported in response to survey conducted under section 71 of CEPA (Environment Canada 2009). See survey for specific inclusions and exclusions (Schedules 2 and 3).

Table 4-2 presents a summary of major uses of L2, L4, L5, D3, and dvTMDS according to information reported pursuant to section 71 survey conducted under CEPA (Environment Canada 2009). Additional uses of these substances in Canada are listed in Table 4-3.

Table 4-2. Summary of major non-confidential uses of L2, L4, L5, D3, and dvTMDS in the Siloxanes Group in Canada reported through CEPA section 71 survey[a] (based on consumer and commercial DSL codes reported by the user)

Major uses	Substance(s)
Adhesives and sealants	D3
Anti-freeze and de-icing products	L2
Drugs	L5[b]
Electrical and electronics	L2
Intermediates	L2, dvTMDS
Medical devices	L2
Personal care products	L2, L4, L5, D3
Paints and coatings	L5

[a] See survey for specific inclusions and exclusions (schedules 2 and 3).
[b] Reported use in drugs was for 'dimethicone', not specifically for L5.

In Canada, L2, L4, L5, and D3 are reported to be used primarily as intermediates, solvents, skin conditioning agents, surface active agents, polymers and functional fluids in products available to consumers as well as in industrial applications such as paints and coatings (Environment Canada 2009). For instance, L2 and D3 are used in cosmetics such as body lotions, face creams, facial make-up, bandage adhesive remover and nail polish drying drops according to the cosmetic notifications (personal communication, emails from Consumer Product Safety Directorate (CPSD), HC to ESRAB, HC, dated January 31, 2017 and July 17, 2017; unreferenced). L2 is also found in liquid spray bandages (MSDS 2017). L4 is found in some cosmetics such as body butters, foot cream sticks and lip balms (MSDS 2014a, 2014b, 2014c). Although L5 is not found in licensed natural health products in Canada (LNHPD 2018), it has been identified in sunscreens available to Canadian consumers (Household Products Database 1993-2016). D3 is found in diaper creams and fragrances (Wang et al. 2009). DvTMDS is primarily used as an intermediate in the manufacture of polymers and other organic compounds, and there is no indication that it is used in products available to consumers in Canada (Environment Canada 2009). Thus, exposure of the general population to dvTMDS from use of products available to consumers is not expected. The OECD (2014) and the dossier submitted to ECHA under REACH (2017c) also reported that dvTMDS is not used in products available to consumers in Europe.

Table 4-3. Additional uses in Canada for L2, L4, L5, D3 and dvTMDS in the Siloxanes Group

Use	L2	L4	L5	D3	dvTMDS
Food packaging materials[a]	N	N	N	N	Y
Medicinal or non-medicinal ingredients in disinfectant, human or veterinary drug products[b]	N	N	N	Y[b]	N
Natural Health Products Ingredients Database[c]	Y	N	N	Y	N
Medicinal or non-medicinal ingredients in licensed natural health products[c]	Y	N	N	N	N
Notified to be present in cosmetics under the *Cosmetic Regulations*[d]	Y	N	N	Y	N
Formulant in registered pest control products[e]	N	Y[e]	Y[e]	Y	N

Abbreviations: Y= use was reported for this substance; N = use was not reported for this substance.

[a] Personal communication, emails from Food Directorate (FD), Health Canada (HC) to Existing Substance Risk Assessment Bureau (ESRAB), HC, dated February 3, 2017, and June 2015 (Food Packaging/Incidental Additive result for dvTMDS only); unreferenced.

[b] Personal communication, emails from Therapeutic Products Directorate (TPD), HC to ESRAB, HC, dated January 25, 2017 and June 2015; unreferenced. Although D3 is used in drug products in Canada, all products are discontinued.

[c] Personal communication, emails from Natural and Non-Prescription Health Products Directorate (NNHPD), HC to ESRAB, HC, dated January 30, 2017 and June 2015; unreferenced. L2 and D3 are listed in the Natural Health Products Ingredients Database with a non-medicinal role for topical use only as skin-conditioning agent in natural health products but D3 has not been found in any products. L2 occurs in one licensed product for topical use.

[d] Personal communication, emails from CPSD, HC to ESRAB, HC, dated January 31, 2017 and July 17, 2017; unreferenced.

[e] Personal communication, email from the Pest Management Regulatory Agency (PMRA), HC to ESRAB, HC, dated February 6, 2017 and June 2015; unreferenced. Although L4 and L5 are on the list of formulants that are found in pest control products currently registered in Canada, there is no record of current use of these substances.

D3 can exist as an impurity or unreacted species in silicone polymers, including the ones used in the manufacture of silicone breast implants. Currently, low molecular weight siloxanes (less than D8 and L6) were not detected (less than 1 µg/g of material) in silicone breast implants sold in Canada (personal communication, email from Medical Devices Bureau, TPD, HC to ESRAB, HC, dated January 25, 2018; unreferenced). Globally, silicone elastomers (polymers with viscoelasticity) are used in a large number of biomedical applications including short- and long-term implants and prostheses, catheters, contact lenses and dentures (Will et al. 2007 cited in Environment Canada, Health Canada 2008a, 2008b, 2008c). On the basis of evidence provided in Canadian submissions for breast implants and literature review, there is no known scientific basis

for any human health concerns for the trace amounts of low molecular weight siloxanes (including D3) in silicone breast implants (personal communication, email from Medical Devices Bureau, HC to ESRAB, HC, dated January 25, 2018; referenced).

Although there were no Canadian manufacturing or import quantities reported for cyclomethicone in 2011 according to a survey conducted under section 71 of CEPA (Environment Canada 2013), cyclomethicone is used in cosmetics, drugs, natural health products, and pesticides, and may be used in food packaging materials and incidental additives [personal communication, email from FD, HC to ESRAB, HC, dated February 3, 2017; personal communication, email from TPD, HC to ESRAB, HC, dated January 25, 2017; personal communication, email from NNHPD, HC to ESRAB, HC, dated January 30, 2017; personal communication, email from CPSD, HC to ESRAB, HC, dated April 1, 2016; personal communication, email from PMRA, HC to ESRAB, HC, dated February 6, 2017; all unreferenced]. Although cyclomethicone was not reported in a section 71 survey conducted in 2011, responses to the notice published under section 71 of CEPA for the 2006 calendar year contained data on the quantity of its major components (D4, D5 or D6) used or imported as CAS RN 69430-24-6 (Environment Canada 2007).

5. Potential to cause ecological harm

5.1 Characterization of Ecological Risk

The ecological risks of the substances in the Siloxanes Group were characterized using the ecological risk classification of organic substances (ERC) approach (ECCC 2016a). The ERC is a risk-based approach that considers multiple metrics for both hazard and exposure, on the basis of weighted consideration of multiple lines of evidence for determining risk classification. The various lines of evidence are combined to discriminate between substances of lower or higher potency and lower or higher potential for exposure in various media. This approach reduces the overall uncertainty with risk characterization compared to an approach that relies on a single metric in a single medium (e.g., median lethal dose) for characterization. The following summarizes the approach, which is described in detail in ECCC (2016a).

Data on physical-chemical properties, fate (chemical half-lives in various media and biota, partition coefficients, and fish bioconcentration), acute fish ecotoxicity, and chemical import or manufacture volume in Canada were collected from the scientific literature, available empirical databases (e.g., OECD QSAR Toolbox 2016), and from responses to surveys conducted under section 71 of CEPA, or they were generated using selected (quantitative) structure-activity relationship ([Q]SAR) or mass-balance fate and bioaccumulation models. These data were used as inputs to other mass-balance models or to complete the substance hazard and exposure profiles.

Hazard profiles were based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Exposure profiles were also based on multiple metrics, including potential emission rate, overall persistence, and long-range transport potential. Hazard and exposure profiles were compared to decision criteria in order to classify the hazard and exposure potentials for each organic substance as low, moderate, or high. Additional rules were applied (e.g., classification consistency, margin of exposure) to refine the preliminary classifications of hazard or exposure.

A risk matrix was used to assign a low, moderate or high classification of potential risk for each substance on the basis of its hazard and exposure classifications. ERC classifications of potential risk were verified using a two-step approach. The first step adjusted the risk classification outcomes from moderate or high to low for substances that had a low estimated rate of emission to water after wastewater treatment, representing a low potential for exposure. The second step reviewed low risk potential classification outcomes using relatively conservative, local-scale (i.e., in the area immediately surrounding a point-source of discharge) risk scenarios, designed to be protective of the environment, to determine whether the classification of potential risk should be increased.

ERC uses a weighted approach to minimize the potential for both over and under classification of hazard, exposure and subsequent risk. The balanced approaches for dealing with uncertainties are described in greater detail in ECCC 2016a. The following describes two of the more substantial areas of uncertainty. Error with empirical or modeled acute toxicity values could result in changes in classification of hazard, particularly metrics relying on tissue residue values (i.e., mode of toxic action), many of which are predicted values from (Q)SAR models. However, the impact of this error is mitigated by the fact that overestimation of median lethality will result in a conservative (protective) tissue residue value used for critical body residue (CBR) analysis. Error with underestimation of acute toxicity will be mitigated through the use of other hazard metrics such as structural profiling of mode of action, reactivity and/or estrogen binding affinity. Changes or errors in chemical quantity could result in differences in classification of exposure as the exposure and risk classifications are highly sensitive to emission rate and use quantity. The ERC classifications thus reflect exposure and risk in Canada based on what is believed to be the current use quantity, and may not reflect future trends.

Critical data and considerations used to develop the substance-specific profiles for the substances in the Siloxanes Group, and the hazard, exposure and risk classification results are presented in ECCC (2016b).

The hazard and exposure classifications for the six substances in the Siloxanes Group are summarized in Table 5-1.

Table 5-1. Ecological risk classification results for the substances in the Siloxanes Group

Common name (abbreviation)	ERC hazard classification	ERC exposure classification	ERC risk classification
Hexamethyldisiloxane (L2)	low	low	low
Decamethyltetrasiloxane (L4)	medium	low	low
Dodecamethylpentasiloxane (L5)	low	low	low
Cyclotrisiloxane (D3)	low	low	low
Divinyltetramethyldisiloxane (dvTMDS)	medium	low	low
Cyclomethicone	low	low	low

On the basis of low hazard and low exposure classifications according to information considered under ERC, L2, L5, D3, and cyclomethicone were classified as having a low potential for ecological risk. It is therefore unlikely that these substances will result in concerns for the environment in Canada.

Cyclomethicone is a UVCB that can contain cyclic siloxanes including D4 (octamethylcyclotetrailoxane, CAS RN: 556-67-2) in unknown amounts. No ecotoxicity data were available for cyclomethicone as a UVCB for the purposes of the ERC analysis. The assessment of low hazard in ERC was based on several hazard descriptors using evidence from all cyclic components of the UVCB. All components of cyclomethicone show low or no acute effects to aquatic organisms, except D4. In a 2008 assessment (Environment Canada, Health Canada 2008a), D4 was found to meet the criteria for ecological concern under paragraph 64(*a*) of CEPA and was subsequently added to Schedule 1 of CEPA in 2011. Based on greater evidence for low acute toxicity of the majority of the components of cyclomethicone, a low level of toxicity was assigned to represent the hazard of cyclomethicone as a UVCB.

According to information considered under ERC, L4 and dvTMDS were classified as having low exposure potentials. L4 and dvTMDS were classified as having moderate hazard potential on the basis of a reactive mode of action and a moderate potential to cause adverse effects in aquatic food webs given their bioaccumulation potential. The potential effects and how they may manifest in the environment were not further investigated due to the low exposure of these substances. On the basis of current use patterns, these substances are unlikely to be resulting in concerns for the environment in Canada.

6. Potential to cause harm to human health

For cyclomethicone, the human health risk characterization was evaluated as part of the D4, D5, and D6 assessments (Environment Canada, Health Canada 2008a, 2008b, 2008c; a revised conclusion on D5 was published in Canada 2012). No significant new studies and no subsequent international reviews for D4, D5, D6 or cyclomethicone were identified, with the exception of a 2015 OECD review of D6 (OECD 2015); which is not

considered to impact the D6 assessment. The remaining five substances in the Siloxanes Group are discussed below.

6.1 Exposure assessment

Exposure of the general population to substances in the Siloxanes Group can result from use of cosmetics and other products available to consumers, and their release to the environment during production, processing, use or disposal of the substances or products containing them. Due to their volatility and widespread use in cosmetic products, inhalation and dermal absorption are considered to be the primary routes of exposure.

6.1.1 Environmental media and food

Linear siloxanes subgroup (L2, L4, L5)

L4 and L5 have been measured in ambient air studies in Canada. L4 and L5 were detected in outdoor air through active sampling in Toronto (2010-2011) at concentrations ranging from 0.0004 to 0.0065 µg/m^3 and 0.0007 to 0.0048 µg/m^3, respectively, with a detection frequency of 100% (Ahrens et al. 2014). Genualdi et al. (2011) also measured the two substances in outdoor air in eight locations across Canada, and the concentration of L4 and L5 ranged from not detected to 0.00066 µg/m^3 and not detected to 0.00045 µg/m^3, respectively, during a study period of about 90 days (samples collected using a passive air sampler).

Substances in the linear siloxanes subgroup have been detected at higher concentrations in ambient air internationally (Kaj et al. 2005a, 2005b; Genualdi et al. 2011; Kierkegaard and MacLachlan 2013; Gallego et al. 2017; ECHA 2018c). Gallego et al (2017) measured L2, L4, and L5 at average concentrations ranging from 0.003 to 0.215 µg/m^3, not detected to 0.012 µg/m^3, and not detected to 0.066 µg/m^3, respectively, in 10 locations in Spain during 2013 to 2015 (total sample size of 271 for each substance). A 90th percentile concentration of 0.2 µg/m^3 for L2 was measured in air near houses in unspecified locations in Europe (sample size of 18) (ECHA 2018c).

As a conservative approach, the highest concentration from Gallego et al (2017) was used in characterizing exposure to L2 (0.215 µg/m^3) via ambient air, and the highest concentrations measured from Ahrens et al (2014) and Genualdi et al (2011) were selected for characterizing exposure of the general population to L4 (0.0065 µg/m^3) and L5 (0.0048 µg/m^3) via ambient air in this assessment report (Tables A-1, A-2, and A-3 in Appendix A).

Levels of siloxanes measured in indoor air were generally higher than those detected in outdoor air. As part of the 2012 to 2013 Canadian Health Measures Survey (CHMS), Zhu (2017) conducted a National Indoor Air Survey of 88 volatile organic compounds in over 4000 Canadian residential dwellings (e.g., houses, apartments) across Canada. L2 was measured at concentrations of 0.032 µg/m^3 as a geometric mean, 0.015

μg/m^3 as a median value, and 0.67 μg/m^3 as the 95th percentile value. L4 was measured at concentrations of 0.664 μg/m^3 as a geometric mean, 0.6 μg/m^3 as a median value, and 1.69 μg/m^3 as the 95th percentile value. L5 was measured at concentrations of 0.77 μg/m^3 as a geometric mean, 0.77 μg/m^3 as a median value, and 0.9 μg/m^3 as the 95th percentile value.

L4 and L5 have been detected in indoor air in the US. Tran and Kannan (2015) reported concentrations of L4 and L5 ranging from not detected to 0.00887 μg/m^3 (28.3% detection frequency) and not detected to 0.106 μg/m^3 (55% detection frequency), respectively, in the vapour phase of indoor air samples collected from 60 different locations in the US in 2014. Siloxanes in this group were also detected in indoor air internationally (Kaj et al. 2005a; Katsoyiannis et al. 2014; Pieri et al. 2013).

As a conservative approach, the 95th percentile values for L2, L4, and L5 from the CHMS study (Zhu 2017) were selected for characterizing exposure via indoor air in this assessment report (Tables A-1, A-2, A-3).

No studies were identified reporting the substances in the linear siloxanes subgroup in drinking water in Canada. However, the siloxanes have been detected in surface water in Europe (Companioni-Damas et al. 2012; Homem et al. 2017) and Japan (Horii et al. 2017). Companioni-Damas et al. (2012) reported the maximum concentration of L2, L4, and L5 among two rivers in Spain at 0.00165 μg/L, 0.0008 μg/L, and 0.00394 μg/L, respectively, in spring of 2011. Homem et al. (2017) reported the maximum concentration of L2, L4, and L5 measured in river water in Sweden at 0.0008 μg/L, 0.0005 μg/L, and 0.004 μg/L, respectively.

As a conservative approach, the maximum concentrations of L2, L4, and L5 reported from the two studies (Companioni-Damas et al 2012; Homem et al 2017) were selected for characterizing exposure to L2, L4, and L5 via drinking water (see Tables A-1, A-2, A-3).

No studies were identified reporting the substances in the linear siloxanes subgroup in soils in Canada. Internationally, L2, L4, and L5 were detected in Europe, Antarctica, and/or Japan (Kaj et al. 2005a,b; Companioni-Damas et al. 2012; Sanchis et al. 2015; ECHA 2018a, 2018b).

No Canadian data on levels of linear siloxanes in dust were identified. In the US, L4 and L5 were detected in floor dust samples from homes, labs, and offices in 2014 at a concentration ranging from 1.5 to 34.2 μg/kg and <3 to 67 μg/kg, respectively. L4 and L5 have also been detected in dust from 2010 to 2014 in other countries including Greece, Romania, China, Colombia, India, Japan, Kuwait, Pakistan, Saudi Arabia, South Korea and Vietnam (Tran et al. 2015; Liu et al. 2018).

As a conservative approach, the maximum concentrations of L4 and L5 reported from the US study were selected for characterizing exposure via dust in this assessment report (Tables A-2 and A-3).

Canadian occurrence data for siloxanes in retail foods and human milk were not identified. In Canada, L2, L4, and L5 were monitored but not detected in biota from the Gulf of St. Lawrence and St. Lawrence River estuary in 2008 (Wang et al. 2017), and in freshwater fish from 16 water bodies across Canada in 2009 and 2010 (McGoldrick et al. 2014). L4 was monitored but not detected (method detection limit of 1.3 to 1.8 µg/kg ww) in any of the sampled fish and shellfish from Lake Ontario, Canada (ECHA 2018a), or in any of the biota samples from Lake Pepin, US, during 2011 to 2013 (ECHA 2018a). L2 and L4 were also monitored but not detected in fish in Sweden and Norway (Kaj et al. 2005a; ECHA 2018a).

A chamber air study in the US reported that L5 was measured with concentrations in the chamber air ranging from 10 to 30 µg/m^3 after opening microwaved popcorn (Rosati et al. 2007). Oral and inhalation exposures to it are expected to be less than from other products or environmental media.

No biomonitoring studies were identified in Canada forL2, L4, or L5. Internationally, concentrations of L2, L4, and L5 have been measured in human breast milk in Europe. The Swedish National Screening Program conducted in 2004 reported mean concentrations of L2 and L4 in human breast milk at 0.005 to 0.006 µg/L and 0.008 to 0.013 µg/L, respectively, while L5 was not detected (Kaj et al. 2005a).

D3

D3 was detected in outdoor air through active sampling in Toronto (2010-2011) at concentrations ranging from 0.0005 to 0.0047 µg/m^3 with a detection frequency of 100% (Ahrens et al. 2014). Genualdi et al. (2011) also measured D3 in outdoor air at concentrations ranging from 0.010 to 0.117 µg/m^3. In Spain, D3 was measured at average concentrations ranging from 0.039 to 1.358 µg/m^3 in 10 locations during 2013 to 2015 (Gallego et al. 2017). Maximum concentration of D3 from Genualdi et al (2011) was selected for characterizing exposure of the general population to D3 (0.117 µg/m^3) via ambient air in this assessment report (Table A-4 in Appendix A).

Indoor air study conducted in a chamber setting in Canada measured D3 at a median concentration of 1 µg/m^3 and the 90th percentile of 9 µg/m^3 (NRC 2011). Internationally, Tran and Kannan (2015) detected D3 in indoor air at concentrations ranging from 0.00346 to 0.0686 µg/m^3 (100% detection frequency) from 60 different locations in the US in 2014. Another study measured D3 at a maximum concentration of 9.3 µg/m^3 in indoor air of schools and early childhood education centers in the US from 2010 to 2011 (Bradman et al. 2015). The highest concentration of D3 (9.3 µg/m^3) reported from Bradman et al. (2015) study was selected for characterizing exposure via indoor air in this assessment report (Table A-4).

No Canadian data on level of D3 in drinking water, soil, and dust were identified. Internationally, Sanchis et al. 2013 cited in Homem et al. 2017 reported the maximum concentration of D3 measured in river water in Sweden at 0.076 µg/L. The maximum concentration of D3 from this study was selected for characterizing exposure to D3 via drinking water (see Table A-4).

D3 was detected in soil in Antarctica (Sanchis et al. 2015). In the US, D3 was detected in floor dust samples from homes, labs, and offices in 2014 at a concentration ranging from <2 to 50.8 µg/kg. D3 has also been detected in dust from 2010 to 2014 in other countries including Greece, Romania, China, Colombia, India, Japan, Kuwait, Pakistan, Saudi Arabia, South Korea and Vietnam (Tran et al. 2015; Liu et al. 2018). The maximum concentration of D3 reported from the US study was selected for characterizing exposure via dust in this assessment report (Table A-4).

In Canada, D3 was detected in the blood of harbour seals at a maximum concentration of 1.43 µg/kg wet weight (ww) from the Gulf of St. Lawrence and St. Lawrence River estuary in 2008 (Wang et al. 2017). Another study measured D3 at concentrations ranging from 0.83 to 1.2 µg/kg ww in whole body homogenates of lake trout and walleye from 16 water bodies across Canada in 2009 and 2010 (McGoldrick et al. 2014). D3 was also monitored in fish in Sweden and Norway, but not detected (Kaj et al. 2005a). The maximum concentration of D3 reported in freshwater fish from McGoldrick et al. (2014) was selected for characterizing exposure via ingestion of food in this assessment report (Table A-4).

Flassbeck et al (2001) detected D3 in the plasma and blood of women who are or were exposed to silicone gel-filled breast implants in Germany.

DvTMDS

While L2, L4, L5, and D3 are detected in various environmental media and/or food, no information was found on dvTMDS present in environmental media or food. Although no monitoring data on dvTMDS have been identified, since dvTMDS is mainly used as an intermediate for manufacturing other compounds or polymers at industrial sites and is not expected to remain after end use (Environment Canada 2009; ECHA 2017e; OECD 2014), its release to the environment is expected to be limited.

In Canada, dvTMDS may be present in certain food packaging materials with direct food contact as a result of its use in the manufacture of silicone materials and release coating. Dietary exposure to dvTMDS from this use is negligible (personal communication, email from FD, HC to ESRAB, HC, dated June 2015 and Jan 2018; unreferenced).

Intake based on environmental media, food and biomonitoring data

Overall, total daily intakes of L2, L4, L5, and D3 from environmental media and food have been estimated to range from 0.12 to 0.37 µg/kg-bw/day, 0.29 to 0.89 µg/kg-

bw/day, 0.16 to 0.47 µg/kg-bw/day, and 1.6 to 4.9 µg/kg-bw/day, respectively, with infants and toddlers aged 6 months to 4 years having the highest intakes for all substances (see Appendix A). Given the absence of soil monitoring and biomonitoring data in Canada and low concentrations of the siloxane substances reported in international biomonitoring studies, exposure was not quantified and oral intakes from ingestion of soil or breast milk were not estimated for the siloxane substances.

According to these intake estimates, inhalation exposure via air accounts for 99.8 to 99.9% of the total daily intake of L2, L4, L5, and D3, and thus potential intake via food, drinking water, dust or soil is considered negligible. Exposure concentrations in indoor air were estimated to be higher than in ambient air. Exposure of the general population to dvTMDS from environmental media and food is considered to be negligible.

6.1.2 Products available to consumers

All substances in the Siloxanes Group, except for dvTMDS, are used in a variety of products available to consumers that may result in exposure to the general population of Canada.

Exposures to the general population from the use of cosmetics and other products available to consumers were characterized using ConsExpo Web (2018) (see Table B-1 in Appendix B). The estimates of exposure to L2, L4, and L5 are summarized in Tables 6-1, 6-2, and 6-3, respectively. On the basis of a study of skin samples taken from six donors and exposed to L2 for 24 hours, L2 showed a very low dermal absorption potential (0.02%) in human skin (Dow Corning Corporation [DCC] 2000 cited in OECD 2013). Although it is expected that L4 and L5 will have lower dermal absorption rates than L2 due to their physical-chemical properties, the same value for dermal absorption is used.

The estimates of exposure to D3 from use of cosmetics and other products available to consumers are presented in Table 6-4. Systemic exposures from dermal exposure for different sentinel scenarios were modelled using the maximum flux (Jmax) approach (Williams et al. 2016) (Appendix C). Inhalation exposure was modelled using ConsExpo Web (2018) (see Table B-1 in Appendix B).

Table 6-1. Estimated potential exposures to L2 from the use of cosmetics and other products available to consumers

Product scenario	Maxi-mum concen-tration[a]	Dermal per event systemic exposure (mg/kg bw)	Inhalation mean event concentration (mg/m^3)[b]	Dermal daily systemic exposure (mg/kg bw/day)
Body lotion for face, neck and neckline (adults)	3%	0.000193	N/A	0.000193
Body lotion for face, neck and neckline (teens)	3%	0.000203	N/A	0.00016
Aerosol bandage adhesive remover (adults)	67%	0.00161	N/A	N/A
Aerosol bandage adhesive remover (teens)	67%	0.00192	N/A	N/A
Facial makeup (adults)	45%	0.000685	N/A	0.00085
Facial makeup (teens)	45%	0.000818	N/A	0.00101
Hair styling product	100%	0.000536	N/A	N/A
Nail polish drying drops (adults, teens)	100%	N/A	13.3	N/A
Aerosol bandage adhesive remover (adults, teens)	67%	N/A	0.729	N/A

Abbreviation: N/A, Not applicable.

[a] Personal communication, emails from CPSD, HC to ESRAB, HC, dated January 31, 2017 and July 17, 2017; unreferenced.

[b] Inhalation mean event concentrations are amortized over a 6-hour period by multiplying it by 'exposure duration/6-hour' to be aligned with the duration of treatment per day (via inhalation) in the toxicity study.

Table 6-2. Estimated potential exposures to L4 from the use of cosmetics and other products available to consumers

Product scenario	Maxi-mum concen-tration	Route of exposure	Per event systemic exposure (mg/kg bw)	Daily systemic exposure (mg/kg bw/ day)
Lip balm (adults)	5%[a]	oral	0.00705	0.0166
Lip balm (teens)	5%[a]	oral	0.00842	0.0202
Lip balm (children)	5%[a]	oral	0.0161	0.0143
Lip balm (toddlers)	5%[a]	oral	0.0323	0.0189

Product scenario	Maxi-mum concen-tration	Route of exposure	Per event systemic exposure (mg/kg bw)	Daily systemic exposure (mg/kg bw/ day)
Body butter for stretch marks (adults)	5%[b]	dermal	0.000532	0.000532
Foot cream stick (adults)	5%[c]	dermal	0.000578	0.000549

[a] MSDS (2014c).
[b] MSDS (2014a).
[c] MSDS (2014b).

Table 6-3. Estimated potential exposures to L5 from the use of products available to consumers

Product scenario	Maximum concen-tration	Inhalation mean event concen-tration (mg/m^3)[b]	Dermal daily Systemic exposure (mg/kg bw/ day)
Sunscreen spray (adults)	10%[a]	N/A	0.00205
Sunscreen spray (teens)	10%[a]	N/A	0.0028
Sunscreen spray (children)	10%[a]	N/A	0.00299
Sunscreen liquid (adults)	10%[a]	N/A	0.00719
Sunscreen liquid (teens)	10%[a]	N/A	0.00858
Sunscreen liquid (children)	10%[a]	N/A	0.00569
Sunscreen spray (adults, teens)	10%[a]	1.23	N/A
Sunscreen spray (children)	10%[a]	0.686	N/A

Abbreviation: N/A, Not applicable.
[a] Household Products Database 1993-2016.
[b] Inhalation mean event concentrations are amortized over a 6-hour period by multiplying it with 'exposure time/6-hour' to be aligned with the duration of inhalation toxicity study.

Table 6-4. Estimated potential exposures to D3 from the use of cosmetics and other products available to consumers

Product scenario (adult, otherwise indicated)	Maximum concen-tration	Dermal systemic exposure (mg/kg bw/ day)[d]	Inhalation mean event concen-tration (mg/m^3)[e]
Body makeup	0.044% [a]	0.330	N/A

Product scenario (adult, otherwise indicated)	Maximum concen-tration	Dermal systemic exposure (mg/kg bw/ day)[d]	Inhalation mean event concen-tration (mg/m^3)[e]
Face cream	5%[b]	0.0233	N/A
Fragrance	0.12 mg/g ww[c]	0.00366	N/A
Diaper cream (toddlers)	0.45 mg/g ww[c]	0.0678	N/A
Diaper cream (infants)	0.45 mg/g ww[c]	0.0893	N/A
Fragrance	0.12 mg/g ww[c]	N/A	2.24E-06

Abbreviation: N/A, Not applicable.

[a] Personal communication, emails from CPSD, HC to ESRAB, HC, dated January 31, 2017 and July 17, 2017; unreferenced.

[b] MSDS (2010).

[c] Wang et al. (2009).

[d] Estimates of dermal systemic exposure to D3 are based on internal dose of D3 on day of exposure and estimated using Jmax method (Williams et al. 2016).

[e] Inhalation estimates are amortized concentration. Inhalation mean event concentrations are amortized over a 6-hour period by multiplying it with 'exposure time/6-hour' to be aligned with the duration of inhalation toxicity study.

6.2 Health effects assessment

Linear siloxanes subgroup (L2, L4, L5)

For the three substances in this subgroup, an international assessment was available for L2 (OECD 2013). Additional information for L2, L4 and L5 was obtained from published literature or studies cited in the European Chemicals Agency (ECHA) database.

A read-across approach wherein data from one substance informed the human health assessments of other substances within this subgroup, was used based on similarities in structure, physical-chemical properties, toxicokinetics, and function. In most cases, the information on L2 was used to predict health effects for L4 and L5 (see Appendix D).

On the basis of oral gavage and inhalation dosing in rats, L2 was found to be mostly eliminated via exhalation whereas a small proportion (< 3%) was excreted as metabolites in the urine (Dow Corning Corporation [DCC] 2008 cited in OECD 2013; ECHA 2016). The major metabolite in urine was identified as 1,3-bis(hydroxymethyl)tetramethyldisiloxane (DCC 2001 cited in OECD 2013; ECHA 2016). In a 15-day repeated dose study in rats (animals exposed nose-only 6 hours/day, 7days/week to ^{14}C-L2), the majority of the radioactivity was eliminated from the body within 24 hours post-exposure (ECHA 2016). For L5, 25% of an oral gavage dose in rats was absorbed in the gastrointestinal tract with 97% of it being eliminated via faeces and expired in air (approximately 23%), and with < 3% recovered in urine. Although no

toxicokinetic data were identified for L4, read-across from L2 and L5 suggests that L4 would also be mostly eliminated via exhalation and excreted via faeces or urine after oral or inhalation dosing (DCC 1985; ECHA 1985).

No adverse effects were observed in rats administered L4 or L5 via gavage for seven days up to a limit dose of 1000 mg/kg bw/day (DCC 2009; ECHA 2009c). No adverse effects were observed in rats administered L2, L4 and L5 via gavage for 28 days (Dow Corning 1990 cited in OECD 2013; ECHA 2010d, 2017a). A NOAEL of 25 mg/kg bw/day was determined in a 28-day rat gavage study, based on protoporphyrin accumulation observed in the liver of male animals administered 250 mg/kg bw/day of L4. At the next dose of 1000 mg/kg bw/day, bile duct proliferation and periportal chronic inflammation were observed. However, no adverse effects were observed in females administered doses up 1000 mg/kg bw/day (ECHA 2010a). Four and 3-day gavage studies conducted in rats to determine estrogenic activity were also negative in animals administered doses up to 1200 mg/kg bw/day of L2 (no effect on uterine weights) and in mice administered doses up to 1000 mg/kg bw/day of L4 (no effect on uterine weights and uterine peroxidase activity), respectively (McKim et al. 2001; He et al. 2003).

In a 1 year study described as a combined repeated dose/carcinogenicity study by the authors, rats were administered 0 or 500 mg/kg bw/day of L4 in the diet. There were decreased absolute and relative adrenal weights in both sexes and increased absolute and relative thyroid weights in males (DCC 1966a).

In an 8 month study described as a combined repeated dose/carcinogenicity study by the authors, rabbits were administered 0 or 500 mg/kg bw/day of L4 in the diet. Effects were observed in the heart and kidney of females (increased pericardial fluid and chronic pyelitis of the kidney pelvis) and decreased relative liver weights and increased relative spleen weights were observed in males (DCC 1966b).

No adverse effects were observed in a 28-day dermal study, in which L2 was applied to the shaved backs of rats (under occlusion for 6 hours/day, 5 days/week) at doses up to 1000 mg/kg bw/day. Although statistically significant decreased liver and kidney weights relative to brain weight were observed in males at 1000 mg/kg bw/day, there were no accompanying histopathological effects observed in the liver, and the kidney weight change was considered to be related to male-specific alpha-2µ-globulin mediated effects, which were considered as not relevant to humans (DCC 1993b cited in OECD 2013).

In a 14-day rat inhalation study (animals exposed via their whole body for 6 hours/day, 5 days/week), a NOAEC of 6652 mg/m^3 was determined for L2 based on lack of toxicological effects at the highest tested concentration. Although there was a dose-related increase in relative kidney weights in males at 3306 and 6652 mg/m^3, which correlated with an increase of hyaline droplet inclusions in the epithelial cells of the kidney proximal convoluted tubules, this condition is considered to be specific to male rats and not significant to human health (DCC 1992; ECHA 1992). In a 28-day rat inhalation study (animals exposed via nose-only for 6 hours/day, 5 days/week), a

LOAEC of 950 mg/m^3 (lowest concentration tested) was determined by the OECD for L2 based on clinical chemistry changes (increased phosphorus levels in females at all concentrations and in males at 3380 mg/m^3 and higher) and changes in the lungs observed in both sexes (slight increases in interstitial inflammation, alveolar macrophage accumulation and leukocyte infiltration with increased incidence and severity at 59,260 mg/m^3) at all concentrations tested (from 950 to 59,260 mg/m^3) (DCC 1997c cited in OECD 2013).

Rats were exposed via inhalation (nose-only) for 6 hours/day, 5 days/week to L2 and L4 in two 90-days studies. For L2, a LOAEC of 140 mg/m^3 was determined based on an increased incidence of reduced testes size and/or flaccid testes in males, histopathological changes in the lungs (increased incidence and severity of multifocal, subpleural, subacute to chronic interstitial inflammation) and kidneys (proteinaceous casts and tubular degeneration) in both sexes, and histopathological changes in testes (tubular atrophy) and vagina (mucification of the vaginal mucosa) at all concentrations (140 to 13,640 mg/m^3)(OECD 2013). After a one month recovery period, inflammation in the lungs was still observed in exposed animals (DCC 1997b cited in OECD 2013). While effects in rats were observed at the lowest concentration of L2 tested in the 28- and 90-day nose-only inhalation studies, the effects observed at 140 mg/m^3 in the 90-day study were not observed in the 28-day study at 950 mg/m^3, suggesting that duration of exposure may be a factor. Other 90-day rat inhalation studies conducted with L2 and L4 (whole body exposure) resulted in NOAECs at the highest concentration tested: 33,100 mg/m^3 for L2 (Cassidy et al. 2001, DCC 1998, 2002 cited in OECD 2013) and 5080 mg/m^3 for L4 (ECHA 2010b).

In a 24 month inhalation study in rats exposed via their whole body for 6 hours/day, 5 days/week to L2 concentrations of 670 to 33,100 mg/m^3, a LOAEC of 670 mg/m^3 was determined based on increased incidence of enlarged testes and Leydig cell tumours in males. No adverse effects were observed in females up to the highest concentration tested (DCC 2005 cited in OECD 2013).

In vitro genotoxicity studies conducted with L2, L4, and L5 were negative in bacterial and mammalian cells (OECD 2013; ECHA 2005, 2010c, 2014). In the only in vivo genotoxicity study; a negative result was observed in rats exposed to intraperitoneal doses of 255 to 1030 mg/kg bw L2 in a micronucleus study (Isquith et al. 1988; OECD 2013).

For L2, in both a 1-generation and a 2-generation reproductive toxicity study, animals were exposed via inhalation (whole body, 6 hours/day, 7 days/week) to concentrations of 670 to 33,100 mg/m^3. Neurotoxicity was examined in the 2-generation reproductive toxicity study in F1 adult females (functional observational battery) and at postnatal day (PND) 20 in F2 pups (functional observational battery, brain morphology). In the 2-generation reproductive toxicity study, there were liver effects (pigment accumulation, chronic inflammation, bile duct hyperplasia) at 10,600 mg/m^3 in the F1 generation adults, with a parental NOAEC of 2700 mg/m^3. In the same study, there were decreased pup body weights (F1 and F2, PNDs 4 to 14) at 10,600 mg/m^3, with an offspring NOAEC at

2700 mg/m^3 (identified by OECD as a developmental NOAEC). At 33,100 mg/m^3, F2 pups demonstrated decreased average and peak acoustic startle response in both sexes, lack of habituation in the locomotor activity assessments and delayed attainment of the surface righting response in females (WIL Research Laboratories Inc. 2006 cited in OECD 2013). The NOAEC for reproductive toxicity was 33,100 mg/m^3 in both studies; the NOAEC for parental and offspring toxicity in the 1-generation reproductive toxicity study was also set at 33,100 mg/m^3 (DCC 1999, WIL Research Laboratories 2000, 2006, and Siddiqui et al. 2000 cited in OECD 2013).

For L4, rats were exposed (6 hours/day, 7 days/week) to concentrations of 0 or 5080 mg/m^3 via inhalation (whole body) in a 1-generation reproductive toxicity study; males were exposed for 15 days prior to the mating period up to the day before necropsy (total 29 to 30 days); females were treated for 15 days prior to the mating period up to and including gestation day 19 (total approximately 42 to 49 days); dams and pups were sacrificed on PND 4. Adult males and females were subjected a Functional Observational Battery during the 4th week of exposure. There was no parental or offspring toxicity. However, the LOAEC for reproductive toxicity was 5080 mg/m^3 based on failure to deliver litters in 3/10 dams (the uterus of these 3 dams was stained to enable counting of possible reabsorbed implant sites but reabsorption was not reported) (ECHA 2007a,b).

D3

A review by the OECD in 2009 informed the health effects characterization of cyclotrisiloxane (D3). Additional information for D3 was obtained from the published literature. However, new data obtained to date do not significantly change the health effects characterization based on OECD (2009).

In a 28-day gavage toxicity study in rats, increased relative and absolute liver weights were observed in both sexes, and decreased mean body weights and food consumption were observed in males, at the lowest dose tested of 1000 mg/kg bw/day (Crofoot et al. 1990 cited in Johnson et al. 2012). In a 14-day oral (gavage) study in rats designed to examine effects in the liver, although liver weights increased in males at 100 mg/kg bw/day and in both sexes above 400 mg/kg bw/day (at the next dose of 1600 mg/kg bw/day), there were no gross pathological changes (Dow Corning 1990 cited in OECD 2009). In the 14- and 28-day studies discussed above, the body and liver weight and food consumption changes may be reversible, based on the absence of gross pathological changes in the liver and similar trends in food consumption and body weight at 1000 mg/kg bw/day or above. However, in the absence of studies with additional analyses (i.e. histopathology), 1000 mg/kg bw/day was conservatively selected as the LOAEL for oral (and dermal) repeated dose studies. Repeated dose dermal toxicity studies were not identified for D3.

In a 28 day inhalation study in rats (nose-only exposure, 6 hours/day, 7 days/week), a NOAEC was established at 945 mg/m^3 on the basis of mortality in both sexes between days 13 and 16 and clinical signs of toxicity (dyspnea, ataxia, reduced reflexes and

piloerection observed on days before death) in animals exposed to 9041 mg/m^3 (LPT 1992 cited in OECD 2009).

There was a 1-generation reproductive toxicity study with D3 (whole body exposure, 6 hours/day, 7 days/week, animals were exposed up to 46 days during mating and pregnancy (28 days in males and up to gestation day 19 in females) with parental males sacrificed on day 29 and parental females and pups sacrificed on PND 4. There was an increased incidence of protein droplet nephropathy in males was observed in animals exposed to 610 mg/m^3. However, on the basis of both the OECD (2009) and Johnson et al. (2012) reviews, the protein droplet nephropathy is not considered to be relevant to human health, and the inhalation NOAEC for systemic toxicity is 4500 mg/m^3 based on several effects observed in animals exposed to 22,800 mg/m^3 (decreased food consumption and body weights, increased liver weights, increased incidence of centrilobular hepatocellular hypertrophy and changes in clinical chemistry parameters in both sexes, and changes in seminal vesicles [decreased organ weight and increased incidence of organ atrophy], and decreased motor activity in the functional observational battery in males).. The OECD identified a NOAEC for reproductive and developmental toxicity of 4500 mg/m^3 based on decreased litter size and implantation sites in animals exposed to 22,800 mg/m^3, as well as a maternal NOAEC of 4500 mg/m^3 based on decreased body weights in females exposed to 22,800 mg/m^3 (DCC 2002 cited in OECD 2009; Johnson et al. 2012).

In vitro genotoxicity studies showed positive and/or equivocal results for both chromosome aberration and DNA damage/repair in mouse lymphoma cells but negative in bacterial cells (Litton Bionetics Inc. 1978 cited in OECD 2009; Isquith et al. 1988 cited in Johnson et al. 2012), and positive results for DNA damage/repair in human breast epithelial cells (Farasani and Darbre 2017). Mutation potential was negative in mouse lymphoma cells and bacterial cells (*Salmonella typhimurium*) (Litton Bionetics Inc. 1978 and Dow Corning 1979 cited in OECD 2009; Isquith et al. 1988 cited in Johnson et al. 2012). Only one in vivo genotoxicity study was identified: a negative result was observed in rats exposed to intraperitoneal doses of 125 to 1080 mg/kg bw in a micronucleus study (Bioassay systems 1982 cited in OECD 2009; Isquith et al. 1988).

DvTMDS

No high hazard classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity, or reproductive toxicity were identified for dvTMDS. It is also not on the European Chemicals Agency's Candidate List of Substances of Very High Concern for Authorisation (ECHA 2017f). Further investigation of the health effects is not warranted at this time given the negligible exposure of dvTMDS to the general Canadian population.

7. Characterization of risk to human health

Cyclomethicone is primarily comprised of three substances previously assessed under CEPA (D4, D5 and D6). For each of these three primary components (D4, D5 and D6), margins of exposure were considered to be adequate to address uncertainties in the health effects and exposure databases (Environment Canada, Health Canada 2008a, 2008b, 2008c; Canada 2012).

Tables 7-1 to 7-4 provide relevant exposure estimates and critical effect levels, as well as resulting margins of exposure (MOEs) for L2, L4, L5 and D3.

Table 7-1. Relevant exposure and critical effect levels for L2, as well as margins of exposure, for determination of risk

Exposure Scenario	Exposure	Critical effect level	Critical health effect endpoint	MOE
Indoor air	0.0007 mg/m^3	LOAEC = 25 mg/m^3_{adj} in 90-day rat inhalation study (nose-only) using L2.[a]	Increased incidence of reduced testes size and/or flaccid testes in males and histopathological changes in the lungs and kidneys of both sexes, testes in males and vagina in females at all concentrations (25 to 2436 mg/m^3_{adj}).	35 700
Inhalation exposure to nail polish drying drops (per event, adults and teens)[b]	13.3 mg/m^3	NOAEC = 6652 mg/m^3 in 2-week rat inhalation study (whole body) using L2.	No adverse effects (highest dose tested).	500

Inhalation exposure to bandage adhesive remover (per event, adults and teens)	0.729 mg/m^3[b]	NOAEC = 6652 mg/m^3 in 2-week rat inhalation study (whole body) using L2	No adverse effects (highest dose tested).	9130

Abbreviations: MOE = Margin of Exposure; adj = Adjusted to account for daily exposures of 24 h.
a. A LOAEC of 140 mg/m^3 was determined in this study. When exposure is amortized to 24 hours/day, 7 days/week, this LOAEC is adjusted to 25 mg/m^3.
b. Exposure concentration was amortized over 6 hours.

For L2, with respect to inhalation exposure, comparison of critical effects to estimates of exposure concentrations in indoor air and from use of bandage remover and nail polish resulted in MOEs that are considered adequate to account for uncertainties in the health effects and exposure databases.

Dermal exposure to L2 from the use of cosmetics was also considered. No adverse health effects were observed in experimental animals whose skin was exposed to doses up to 1000 mg/kg bw/day of L2 under occlusion in a four-week dermal toxicity study (DCC 1993b cited in OECD 2013). As such, there is a low potential risk to human health from dermal exposure to L2.

Table 7-2. Relevant exposure and critical effects levels for L4, as well as margins of exposure, for determination of risk

Exposure Scenario	Exposure	Critical effect level	Critical health effect endpoint	MOE
Indoor air	0.0017 mg/m^3	LOAEC = 25 mg/m$^3_{adj}$ in 90-day rat inhalation study (nose-only) using L2 (read-across)	Increased incidence of reduced testes size and/or flaccid testes in males and histopathological changes in the lungs and kidneys of both sexes, testes in males and vagina in females at all concentrations (140 to 13,640 mg/m^3).	14 700[a]

Oral daily exposure to lip balm (teens)	0.0202 mg/kg bw/day	NOAEL = 25 mg/kg bw/day in 28-day rat gavage study using L4.	Protoporphyrin accumulation in the liver at 250 mg/kg bw/day.	1240
Oral per event exposure to lip balm (toddlers)	0.0323 mg/kg bw	NOAEL = 25 mg/kg bw/day in 28-day rat gavage study using L4.	Protoporphyrin accumulation in the liver at 250 mg/kg bw/day.	774

Abbreviations: MOE = Margin of Exposure; adj = Adjusted to account for daily exposures of 24 h.

[a] The LOAEC in the 90-day study in rats exposed to L4 was not selected for use in consideration of the study protocol (whole body exposure and daily exposure duration not specified). Comparison of exposure to the 24 hours/day time-weighted adjusted LOAEC of 1270 mg/m^3 in the 1-generation reproduction study (initially LOAEC of 5080 mg/m^3 based on increased failure to deliver litters) would result in a MOE of 747 000. This study was not selected for use, also in consideration of the study protocol (whole body exposure and shorter duration than the 90-day study using L2 [<=53 days]).

For L4, with respect to inhalation and oral exposure, comparison of critical effect levels and estimates of exposure from indoor air and use of lip balm resulted in MOEs that are considered adequate to account for uncertainties in the health effects and exposure databases.

Dermal exposure to L4 from the use of cosmetics was also considered. No adverse health effects were observed in experimental animals whose skin was exposed to doses up to 1000 mg/kg bw/day of L2 under occlusion in a four-week dermal toxicity study (DCC 1993b cited in OECD 2013). L2 is considered to be an adequate analogue of L4 and information on L2 was used to predict potential health effects of L4. As such, there is a low potential risk to human health from dermal exposure to L4.

Table 7-3. Relevant exposure and critical effects levels for L5, as well as margins of exposure, for determination of risk

Exposure Scenario	Exposure	Critical effect level	Critical health effect endpoint	MOE
Indoor air	0.0009 mg/m^3	LOAEC = 25 mg/m$^3_{adj}$ in 90-day rat inhalation study (nose-only) using L2 (read-across).	Increased incidence of reduced testes size and/or flaccid testes in males and histopathological changes in the lungs and kidneys of both sexes, testes in males and vagina in females at all concentrations	27 800

			(140 to 13,640 mg/m^3).	
Inhalation exposure to sunscreen spray (per event, adults, teens)	1.23 mg/m^{3a}	NOAEC = 6652 mg/m^3 in 2-week rat inhalation study (whole body) using L2 (read-across).	No adverse effects (highest dose tested).	5400

Abbreviations: MOE, Margin of Exposure.
a. Exposure concentration was amortized over 6 hours.

For L5, with respect to inhalation exposure, comparison of critical effects with estimates of exposure from indoor air and the use of sunscreen spray resulted in MOEs that are considered adequate to account for uncertainties in the health effects and exposure databases.

Dermal exposure to L5 from the use of sunscreens was also considered. No adverse health effects were observed in experimental animals whose skin was exposed to doses up to 1000 mg/kg bw/day of L2 under occlusion in a four-week dermal toxicity study (DCC 1993b cited in OECD 2013). L2 is considered to be an adequate analogue of L5 and information on L2 was used to predict potential health effects of L5. As such, there is a low potential risk to human health from dermal exposures to L5.

Table 7-4. Relevant exposure and hazard values for D3, as well as margins of exposure, for determination of risk

Exposure Scenario	Systemic Exposure	Critical effect level	Critical health effect endpoint	MOE
Food, beverages and drinking water	0.00001 mg/kg bw/day	LOAEL = 1000 mg/kg bw/day (LTD) in 28-dayrat gavage study.	Increased relative and absolute liver weights in both sexes and decreased mean body weights and food consumption in males.	100 000 000
Indoor air	0.0093 mg/m^3	NOAEC = 236 mg/m$^3_{adj}$ in 28-day rat inhalation study (nose-only).[c]	Mortality and clinical signs of toxicity in males at 9041 mg/m^3.	25 400
Dermal daily exposure to	0.330 mg/kg bw/day[b]	LOAEL = 1000 mg/kg bw/day (LTD) in 28-day	Increased relative and absolute liver weights in both	3 030

body makeup (adults)		rat gavage study.[d]	sexes and decreased mean body weights and food consumption in males.	
Dermal daily exposure to diaper cream (infants[a])	0.0893 mg/kg bw/day[b]	LOAEL = 1000 mg/kg bw/day (LTD) in 28-day gavage rat study.[d]	Increased relative and absolute liver weights in both sexes and decreased mean body weights and food consumption in males.	11 200

Abbreviations: MOE, margin of exposure; LTD, lowest tested dose; adj, adjusted to account for daily exposures of 24 hours.

[a] Infants refer to the age group of 0 to 0.5 years of age.

[b] Using the Jmax method.

[c] A NOAEC of 945 mg/m^3 was determined in this study. When exposure is amortized to 24 hours/day, this NOAEC is adjusted to 236 mg/m^3.

[d] Although the same 28-day oral study in rats was used for comparison to the oral and dermal exposure estimates, the Health Effects section notes that the effects at 1000 mg/kg bw/day or higher may be reversible.

For D3, the MOEs listed above for the environmental media, food, indoor air, daily and per event dermal or inhalation exposures to cosmetic products scenarios, and daily and per event dermal exposures to diaper cream are all considered adequate to account for uncertainties in the health effects and exposure databases.

For dvTMDS, there is low concern for risk because exposure to the general population of Canada is not expected and there are no high hazard classifications for this substance.

7.1 Uncertainties in evaluation of risk to human health

The key sources of uncertainty are presented in the table below.

Table 7-5. Sources of uncertainty in the risk characterization

Key sources of uncertainty	Impact
No dermal absorption data for L4, L5 and D3.	+
No repeated dose dermal toxicity study for D3.	+/-
No Canadian data in drinking water, soil and dust for substances in the Siloxanes Group.	+/-
For L4, L5, and D3, there are no carcinogenicity studies by any route of exposure. There is also no chronic oral or dermal study for L2.	+/-

+ = uncertainty with potential to cause over-estimation of exposure/risk; +/- = unknown potential to cause over or under estimation of risk.

8. Conclusion

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from L2, L4, L5, D3, dvTMDS and cyclomethicone. It is proposed to conclude that the six substances in the Siloxanes Group do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that the six substances in the Siloxanes Group do not meet the criteria under paragraph 64(*c*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is proposed to conclude that L2, L4, L5, D3, dvTMDS and cyclomethicone do not meet any of the criteria set out in section 64 of CEPA.

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Appendices

Appendix A. Deterministic estimates of daily human exposure to siloxanes in environmental media and food

Table A-1. Estimates of daily intake (µg/kg-bw per day) of L2 by various age groups

Route of exposure	0–6 months[a] breast fed	0–6 months[a] formula fed	0–6 months[a] not formula fed	0.5–4 years[b]	5–11 years[c]	12–19 years[d]	20–59 years[e]	60+ years[f]
Ambient Air[g]	7.5E-03	7.5E-03	7.5E-03	1.6E-02	1.3E-02	7.1E-03	6.1E-03	5.3E-03
Indoor Air[h]	1.6E-01	1.6E-01	1.6E-01	3.5E-01	2.7E-01	1.6E-01	1.3E-01	1.2E-01
Drinking Water[i]	nil	1.8E-04	6.6E-05	7.5E-05	5.9E-05	3.3E-05	3.5E-05	3.7E-05
Total Intake	**1.7E-01**	**1.7E-01**	**1.7E-01**	**3.7E-01**	**2.9E-01**	**1.6E-01**	**1.4E-01**	**1.2E-01**

[a] Assumed to weigh 7.5 kg, to drink 0.0-0.8 L of water per day, to consume 25.7 g of meat & poultry per day (non breast milk-fed only) and 0 g of fish per day (Health Canada 1998), and to ingest 0.038 g of dust per day (Wilson et al. 2013).

[b] Assumed to weigh 15.5 kg, to drink 0.7 L of water per day, to consume 70.1 g of meat & poultry per day and 54.7 g of fish per day (Health Canada 1998), and to ingest 0.041 g of dust per day (Wilson et al. 2013).

[c] Assumed to weigh 31.0 kg, to drink 1.1 L of water per day, to consume 100.1 g of meat & poultry per day and 89.8 g of fish per day (Health Canada 1998), and to ingest 0.031 g of dust per day (Wilson et al. 2013).

[d] Assumed to weigh 59.4 kg, to drink 1.2 L of water per day, to consume 147.4 g of meat & poultry per day and 97.3 g of fish per day (Health Canada 1998), and to ingest 0.002 g of dust per day (Wilson et al. 2013).

[e] Assumed to weigh 70.9 kg, to drink 1.5 L of water per day, to consume 167.8 g of meat & poultry per day and 111.7 g of fish per day (Health Canada 1998), and to ingest 0.0025 g of dust per day (Wilson et al. 2013).

[f] Assumed to weigh 72.0 kg, to drink 1.6 L of water per day, to consume 108.4 g of meat & poultry per day and 72.9 g of fish per day (Health Canada 1998), and to ingest 0.0025 g of dust per day (Wilson et al. 2013).

[g] No monitoring data of ambient air in Canada were identified. The intake was estimated using data collected in industrialized urban areas of Spain as surrogate data to representat ambient air levels in Canada (mean 0.0368 µg/m^3 and sample size of 271; Gallego et al. 2017). The maximum concentration (0.215 µg/m^3) was selected for deriving estimates of daily intake from ambient air exposure.

[h] Indoor air intake was estimated using data from the Canadian Health Measures Survey (median 0.015 µg/m^3 and mean 0.754 µg/m^3; Zhu 2017). The estimates were derived using the 95th percentile concentration (0.67 µg/m^3).

[i] No data on monitoring of drinking water in Canada were identified. The maximum concentration (0.00165 µg/L), measured in the Besos River in Barcelona (Companioni-Damas et al. 2012), was selected for deriving estimates of daily intake from drinking water. This Spanish study was used as surrogate data to representat drinking water concentrations in Canada (mean 0.00132 µg/L and median 0.00137 µg/L).

Table A-2. Estimates of daily intake (µg/kg-bw per day) of L4 by various age groups

Route of exposure	0–6 months[a] breast fed	0–6 months[a] formula fed	0–6 months[a] not formula fed	0.5–4 years[b]	5–11 years[c]	12–19 years[d]	20–59 years[e]	60+ years[f]
Ambient Air[g]	2.3E-04	2.3E-04	2.3E-04	4.9E-04	3.8E-04	2.2E-04	1.9E-04	1.6E-04
Indoor Air[h]	4.1E-01	4.1E-01	4.1E-01	8.9E-01	6.9E-01	3.9E-01	3.4E-01	2.9E-01
Drinking Water[i]	nil	8.5E-05	3.2E-05	3.6E-05	2.8E-05	1.6E-05	1.7E-05	1.8E-05
Dust[j]	1.7E-04	1.7E-04	1.7E-04	9.0E-05	3.4E-05	1.3E-06	1.2E-06	1.2E-06
Total Intake	**4.1E-01**	**4.1E-01**	**4.1E-01**	**8.9E-01**	**6.9E-01**	**3.9E-01**	**3.4E-01**	**2.9E-01**

[a] Assumed to weigh 7.5 kg, to drink 0.0-0.8 L of water per day, to consume 25.7 g of meat & poultry per day (non breast milk-fed only) and 0 g of fish per day (Health Canada 1998), and to ingest 0.038 g of dust per day (Wilson et al. 2013)

[b] Assumed to weigh 15.5 kg, to drink 0.7 L of water per day, to consume 70.1 g of meat & poultry per day and 54.7 g of fish per day (Health Canada 1998), and to ingest 0.041 g of dust per day (Wilson et al. 2013).

[c] Assumed to weigh 31.0 kg, to drink 1.1 L of water per day, to consume 100.1 g of meat & poultry per day and 89.8 g of fish per day (Health Canada 1998), and to ingest 0.031 g of dust per day (Wilson et al. 2013).

[d] Assumed to weigh 59.4 kg, to drink 1.2 L of water per day, to consume 147.4 g of meat & poultry per day and 97.3 g of fish per day (Health Canada 1998), and to ingest 0.002 g of dust per day (Wilson et al. 2013).

[e] Assumed to weigh 70.9 kg, to drink 1.5 L of water per day, to consume 167.8 g of meat & poultry per day and 111.7 g of fish per day (Health Canada 1998), and to ingest 0.0025 g of dust per day (Wilson et al. 2013).

[f] Assumed to weigh 72.0 kg, to drink 1.6 L of water per day, to consume 108.4 g of meat & poultry per day and 72.9 g of fish per day (Health Canada 1998), and to ingest 0.0025 g of dust per day (Wilson et al. 2013).

[g] Ambient air monitoring data (mean 0.0021 µg/m^3, median 0.0017 µg/m^3 and sample size of 70) were based on samples from a semi urban meteorological station in Toronto, Ontario (Ahrens et al. 2014). The maximum concentration (0.0065 µg/m^3) was selected for deriving estimates of daily intake for ambient air exposure.

[h] Indoor air intake was estimated using data from the Canadian Health Measures Survey (median 0.6 µg/m^3 and mean 0.925 µg/m^3; Zhu 2017). The estimate was derived using the 95th percentile concentration (1.69 µg/m^3).

[i] No monitoring data of drinking water in Canada were identified. The maximum concentration (0.0008 µg/L), measured in the Besos River in Barcelona (Companioni-Damas et al. 2012), was selected for deriving estimates of daily intake for drinking water exposure. This Spanish study is considered to be representative of Canada (mean 0.00057 µg/L and median 0.00075 µg/L).

[j] No monitoring data of dust in Canada were identified. The intake was estimated using US data, with samples taken from the floors of homes, offices and labs in Albany, New York (mean 4.79 µg/kg and n = 22 samples; Tran et al. 2015). The maximum value (34.2 µg/kg) was used to derive estimates of daily intake for dust exposure.

Table A-3. Estimates of daily intake (µg/kg-bw per day) of L5 by various age groups

Route of exposure	0–6 months[a] breast fed	0–6 months[a] formula fed	0–6 months[a] not formula fed	0.5–4 years[b]	5–11 years[c]	12–19 years[d]	20–59 years[e]	60+ years[f]
Ambient Air[g]	1.7E-04	1.7E-04	1.7E-04	3.6E-04	2.8E-04	1.6E-04	1.4E-04	1.2E-04
Indoor Air[h]	2.2E-01	2.2E-01	2.2E-01	4.7E-01	3.7E-01	2.1E-01	1.8E-01	1.6E-01
Drinking Water[i]	nil	4.2E-04	1.6E-04	1.8E-04	1.4E-04	8.0E-05	8.3E-05	8.8E-05
Dust[j]	3.4E-04	3.4E-04	3.4E-04	1.8E-04	6.7E-05	2.5E-06	2.4E-06	2.3E-06
Total Intake	**2.2E-01**	**2.2E-01**	**2.2E-01**	**4.7E-01**	**3.7E-01**	**2.1E-01**	**1.8E-01**	**1.6E-01**

[a] Assumed to weigh 7.5 kg, to drink 0.0-0.8 L of water per day, to consume 25.7 g of meat & poultry per day (non breast milk-fed only) and 0 g of fish per day (Health Canada 1998), and to ingest 0.038 g of dust per day (Wilson et al. 2013)

[b] Assumed to weigh 15.5 kg, to drink 0.7 L of water per day, to consume 70.1 g of meat & poultry per day and 54.7 g of fish per day (Health Canada 1998), and to ingest 0.041 g of dust per day (Wilson et al. 2013).

[c] Assumed to weigh 31.0 kg, to drink 1.1 L of water per day, to consume 100.1 g of meat & poultry per day and 89.8 g of fish per day (Health Canada 1998), and to ingest 0.031 g of dust per day (Wilson et al. 2013).

[d] Assumed to weigh 59.4 kg, to drink 1.2 L of water per day, to consume 147.4 g of meat & poultry per day and 97.3 g of fish per day (Health Canada 1998), and to ingest 0.002 g of dust per day (Wilson et al. 2013).

[e] Assumed to weigh 70.9 kg, to drink 1.5 L of water per day, to consume 167.8 g of meat & poultry per day and 111.7 g of fish per day (Health Canada 1998), and to ingest 0.0025 g of dust per day (Wilson et al. 2013).

[f] Assumed to weigh 72.0 kg, to drink 1.6 L of water per day, to consume 108.4 g of meat & poultry per day and 72.9 g of fish per day (Health Canada 1998), and to ingest 0.0025 g of dust per day (Wilson et al. 2013).

[g] Ambient air monitoring data (mean 0.0019 µg/m^3, median 0.0016 µg/m^3, and sample size of 70) were based on samples from a semi urban meteorological station in Toronto, Ontario (Ahrens et al. 2014). The maximum concentration (0.0048 µg/m^3) was selected for deriving estimates of daily intake for ambient air exposure.

[h] Indoor air intake was estimated using data from the Canadian Health Measures Survey (median 0.77 µg/m^3 and mean 0.8 µg/m^3; Zhu 2017). The estimate was derived using the 95th percentile concentration (0.9 µg/m^3).

[i] No monitoring data of drinking water in Canada were identified. The maximum concentration (0.00394 µg/L), measured in the Llobregat River in Barcelona (Companioni-Damas et al. 2012), was selected for deriving estimates of daily intake for drinking water exposure. This Spanish study is considered to be representative of Canada (mean 0.00219 µg/L, median 0.00198 µg/L, and 7 samples with 3 repetitions per sample).

[j] No monitoring data of dust in Canada were identified. The intake was estimated using data from the US, with samples taken from the floor of homes, labs and offices in Albany, New York (mean 8.85 µg/kg and sample size of 22; Tran et al. 2015). The maximum value of 67 µg/kg was used to deriveestimates of daily intake for dust exposure.

Table A-4. Estimates of daily intake (µg/kg-bw per day) of D3 by various age groups

Route of exposure	0–6 months [a] breast fed	0–6 months [a] formula fed	0–6 months [a] not formula fed	0.5–4 years[b]	5–11 years[c]	12–19 years[d]	20–59 years[e]	60+ years[f]
Ambient Air[g]	4.1E-03	4.1E-03	4.1E-03	8.8E-03	6.8E-03	3.9E-03	3.3E-03	2.9E-03
Indoor Air[h]	2.3E+00	2.3E+00	2.3E+00	4.9E+00	3.8E+00	2.2E+00	1.9E+00	1.6E+00
Drinking Water[i]	nil	8.1E-03	3.0E-03	3.4E-03	2.7E-03	1.5E-03	1.6E-03	1.7E-03
Food and Beverages[j]	nil	nil	nil	4.2E-03	3.5E-03	2.0E-03	1.9E-03	1.2E-03
Dust[k]	2.6E-04	2.6E-04	2.6E-04	1.3E-04	5.1E-05	1.9E-06	1.8E-06	1.8E-06
Total Intake	**2.3E+00**	**2.3E+00**	**2.3E+00**	**4.9E+00**	**3.8E+00**	**2.2E+00**	**1.9E+00**	**1.6E+00**

[a] Assumed to weigh 7.5 kg, to drink 0.0-0.8 L of water per day, to consume 25.7 g of meat & poultry per day (non breast milk-fed only) and 0 g of fish per day (Health Canada 1998), and to ingest 0.038 g of dust per day (Wilson et al. 2013)

[b] Assumed to weigh 15.5 kg, to drink 0.7 L of water per day, to consume 70.1 g of meat & poultry per day and 54.7 g of fish per day (Health Canada 1998), and to ingest 0.041 g of dust per day (Wilson et al. 2013).

[c] Assumed to weigh 31.0 kg, to drink 1.1 L of water per day, to consume 100.1 g of meat & poultry per day and 89.8 g of fish per day (Health Canada 1998), and to ingest 0.031 g of dust per day (Wilson et al. 2013).

[d] Assumed to weigh 59.4 kg, to drink 1.2 L of water per day, to consume 147.4 g of meat & poultry per day and 97.3 g of fish per day (Health Canada 1998), and to ingest 0.002 g of dust per day (Wilson et al. 2013).

[e] Assumed to weigh 70.9 kg, to drink 1.5 L of water per day, to consume 167.8 g of meat & poultry per day and 111.7 g of fish per day (Health Canada 1998), and to ingest 0.0025 g of dust per day (Wilson et al. 2013).

[f] Assumed to weigh 72.0 kg, to drink 1.6 L of water per day, to consume 108.4 g of meat & poultry per day and 72.9 g of fish per day (Health Canada 1998), and to ingest 0.0025 g of dust per day (Wilson et al. 2013).

[g] The maximum measured concentration (0.117 µg/m^3; Genauldi et al. 2017) was selected for deriving estimates of ambient air exposure in Canada. This sample was taken from Whistler, British Colombia, and was the highest value among the 8 cross-Canadian sites that were monitored.

[h] No monitoring data of indoor air in Canada were identified. The maximum concentration (9.3 µg/m^3; Bradman et al. 2015) was selected for deriving estimates of indoor air exposure. Samples were taken from schools and early childhood education centers in California, US (geometric mean of 2.3 µg/m^3 and arithmetic mean of 3.0 µg/m^3, and sample size of 34).

[i] No monitoring data of drinking water in Canada were identified. The maximum value of 0.076 µg/L (Sanchis et al. 2013 cited in Homem et al. 2017) was selected for deriving estimates. The water samples were taken from 3 sites on the Llobregat River and 3 at Rubi Brook in Catalonia, Spain (midpoint value of 0.051 µg/L).

[j] Canadian occurrence data for siloxanes in retail foods and human milk were not identified. The intakes from food ingestion were estimated using fish monitoring data in Canada (whole body homogenates of freshwater fishes, range of 0.83 to 1.2 µg/kg ww; McGoldrick et al. 2014). Maximum concentration was selected for deriving estimates of food exposure.

[k] No monitoring data of dust in Canada were identified. The intake was estimated using US data, with samples taken from the floor of homes, labs and offices in Albany, New York (mean 15.8 µg/kg and

sample size of 22; Tran et al. 2015). The maximum value of 50.8 µg/kg was used to derive estimates of daily intake for dust exposure.

Appendix B. Parameters used to estimate human exposures

Exposure from the use of cosmetics was estimated using ConsExpo Web (2018). Exposure estimates were calculated based on default body weights of 70.9 kg, 59.4 kg, 31.0 kg, 15.5 kg, and 7.5 kg for adults (20 years and older), teens (12 to 19 years old), children (5 to 11 years old), toddlers (6 months to 4 years old), and infants (0 to 6 months old), respectively (Health Canada 1998). The parameters used in the estimation of inhalation and dermal exposure from the use of cosmetics are described in Table B-1. Unless specified, the defaults come from the relevant ConsExpo Fact Sheet for the scenario presented.

Table B-1. Exposure parameter inputs for cosmetic scenarios

Product scenario (substance)	Assumptions[a]
Body lotion for face, neck and neckline (L2)	Concentration of L2: 3%[b] Dermal - Direct contact, instant application model Frequency: 1 per day for adults, 0.8 per day for teens (Ficheux et al. 2015; Wu et al. 2010) Exposed area: 3820 cm² for adults, 3410 cm² for teens (considered surface area of face and half of body trunk based on product description; adjustment from Health Canada 1995) Product amount: 2.28 g/use for adults, 2.01 g/use for teens (Ficheux et al. 2016 and SA adjustment from adults) Absorption model: Fixed fraction Absorption fraction: 0.02%
Aerosol bandage adhesive remover (L2)	Concentration of L2: 67%[b] Frequency: 4 per month (professional judgement) Inhalation - Exposure to vapour, instantaneous release Exposure duration: 5 minute (based on fragrance scenario) Product amount: 0.85 g [b] Room volume: 10 m³ Ventilation rate: 2 per hour Inhalation rate: 16.2 m³/hr Dermal - Direct contact, instant application Exposed area: 9 cm² (professional judgement) Product amount: 0.85 g [b] Absorption model: Fixed fraction Absorption fraction: 0.02%
Facial makeup (solid powder; L2)	Concentration of L2: 45% [b] Dermal - Direct contact, instant application model

	Frequency: 1.24 per day for adults and teens (Loretz et al. 2006) Exposed area: 637 cm² for adults and teens(Health Canada 1995) Product amount: 0.54 g/use for adults and teens (Loretz et al. 2006) Absorption model: Fixed fraction Absorption fraction: 0.02%
Hair styling product (hair gel; L2)	Concentration of L2: 100%[b] RF of 0.1 was applied (wash off), giving the final weight fraction of 10% (SCCS 2012) Dermal – Direct contact, instant application model Frequency: 16.4 per month Exposed area: 1092.5 cm² (Health Canada 1995) Product amount: 1.9 g/use for adults Absorption model: Fixed fraction Absorption fraction: 0.02%
Nail polish drying drops (top coat scenario; L2)	Concentration of L2: 100%[b] Inhalation – Exposure to vapour, evaporation model Frequency: 0.18 per day for adults, 0.2 per day for teens (Ficheux et al. 2014) Exposure duration: 18 minutes (Ficheux et al. 2014) Product amount: 0.33 g for adults and teens (Ficheux et al. 2014) Room volume: 1 m^3 (close to the face) Ventilation rate: 1 per hour Inhalation rate: 16.2 m³/day for adults, 15.8 m³/day for teens (Health Canada 1998) Mass transfer coefficient: 10 m/hr Release area mode: constant Release area: 26.2 cm^2 (based on data from Ficheux et al. 2014 and assumption that both finger- and toe-nails are painted) Molecular weight matrix: 124 g/mol
Lip balm (L4)	Concentration of L4: 5% (MSDS 2014c) Oral – Direct product contact, direct oral intake model Frequency: 2.35 per day for adults and teens, 6.2 per week for children, and 4.1 per week for toddlers (Loretz et al. 2005) Amount ingested: 0.01g/application (Loretz et al. 2005; assume 100% of product amount is ingested)

Body butter for stretch mark (body lotion scenario; L4)	Concentration of L4: 5% (MSDS 2014a) Dermal - Direct contact, instant application model Frequency: 1 per day (Loretz et al. 2005) Exposed area: 6370 cm² (considered SA of body trunk based on its use on abdominal area, Health Canada 1998) Product amount: 3.77 g (Loretz et al. 2005, SA adjusted) Absorption model: Fixed fraction Absorption fraction: 0.02%
Foot cream stick (L4)	Concentration of L4: 5% (MSDS 2014b) Dermal – Direct contact, instant application model Frequency: 0.95 per day (Loretz et al. 2005) Exposed area: 1275 cm² (Health Canada 1995) Product amount: 4.1 g for adults (Ficheux et al. 2016) Absorption model: Fixed fraction Absorption fraction: 0.02%
Sunscreen spray (L5)	Concentration of L5: 10% (Household Products Database 1993-2016) Frequency: 1.4 per day for adults, and 1.6 per day for teens and children (Ficheux et al. 2015) Inhalation – Exposure to vapour, instantaneous release model Exposure duration: 10 minute (Health Canada 1998) Product amount: 5.2 g for adults and teens, and 2.9 g for children (Ficheux et al. 2016) Room volume: 10 m³ Ventilation rate: 2 per hour Inhalation rate: 16.2 m³/day (Health Canada 1998) Dermal – Direct contact, instant application model Exposed area: 14000 cm² for adults and teens (Ficheux et al. 2016) and 8450 cm^2 for children (Health Canada 1995) Product amount: 5.2 g for adults and teens, and 2.9 g for children (Ficheux et al. 2016) Absorption model: Fixed fraction Absorption fraction: 0.02%
Sunscreen liquid (L5)	Concentration of L5: 10% (Household Products Database 1993-2016) Frequency: 1.4 per day for adults, teens and children (Ficheux et al. 2015) Dermal - Direct contact, instant application model

	Exposed area: 14000 cm² for adults and teens (Ficheux et al. 2016) and 8450 cm^2 for children (Health Canada 1995) Product amount: 18.2 g/use for adults and teens, and 6.3 g for children (Ficheux et al. 2016) Absorption model: Fixed fraction Absorption fraction: 0.02%
Body makeup (D3)	Concentration of D3: 0.044%[b] Dermal - Direct contact, instant application model (body lotion model was used) Frequency: 1 per day for adults (Ficheux et al. 2015; Wu et al. 2010) Exposed area: 9008 cm² for adults (considered SA of face, arms, and legs based on its use; Health Canada 1995) Product amount: 5.33 g/use for adults (adjusted based on the refined SA; Ficheux et al. 2016) Absorption model: Fixed fraction Absorption fraction: 100%
Face cream (D3)	Concentration of D3: 5% (MSDS 2010) Dermal – Direct contact, instant application model Frequency: 1.8 per day (Loretz et al. 2005) Exposed area: 638 cm² for adults, 730 cm² for teens (Health Canada 1995) Product amount: 1.2 g/use for adults and teens (Loretz et al. 2005) Absorption model: Fixed fraction Absorption fraction: 100%
Fragrance (D3)	Concentration of D3: 0.012% (converted from 0.12 mg/g ww, Wang et al. 2009) Frequency: 1.7 per day (Loretz et al. 2006) Inhalation – Exposure to spray, spraying model Spray duration: 0.08 minute Exposure duration: 5 minute Room volume: 10 m³ Room height: 2.5 m Ventilation rate: 2 per hour Inhalation rate: 16.2 m³/day (Health Canada 1998) Cloud volume: 0.0625 m³ Mass generation rate: 0.1 g/s Airborne fraction: 0.02 Density non-volatile: 1.5 g/cm³ Inhalation cut off diameter: 15 µm Median diameter: 2.7µm

	Arithmetic coefficient of variation: 0.73 Maximum diameter: 50 µm Dermal – Direct contact, instant application model Exposed area: 100 cm² Product amount: 0.33 g/use (Loretz et al. 2006) Absorption model: Fixed fraction Absorption fraction: 100%
Diaper cream (toddlers and infants; D3)	Concentration of D3: 0.045% (converted from 0.45 mg/g ww, Wang et al. 2009) Dermal – Direct contact, instant application model Frequency: 2.6 per day for toddlers and 1.1 per day for infants (Gomez-Berrada et al. 2013) Exposed area: 405 cm² for toddlers and 258 cm² for infants (calculated) Product amount: 2 g for toddlers and 2.6 g for infants (Gomez-Berrada et al. 2013) Absorption model: Fixed fraction Absorption fraction: 100%

[a] Unless specified, a retention factor of 1 was used

[b] Personal communication, emails from CPSD, HC to ESRAB, HC, dated January 31, 2017, July 17, 2017, and April 3, 2018; unreferenced.

Appendix C. Maximum flux (Jmax) approach for estimation of dermal systemic exposures to D3

The maximum flux (Jmax) approach as conducted in Williams et al. (2016) was used to estimate dermal systemic exposures to D3 from use of cosmetics. Face cream scenario is presented below as a representative for this approach. Exposure parameter assumptions for other products containing D3 are the same as described in Table B-1.

The equations used are provided below. Values for water solubility, log Kow, and molecular weight (MW) were obtained from Table 3-1 of this screening assessment report (where available, experimental values were used). A mass balance check was also done for this scenario; see Table C-2 below.

(1) Kp (Potts & Guy equation, based on aqueous vehicle):
Log Kp (in cm/h) = -2.71 + (0.71)(log Kow) - (0.0061)(MW, in g/mol)

(2) Jmax:
Jmax (in mg/cm^2/h) = Kp (in cm/h) x Water solubility (in mg/cm^3)

(3) Maximum theoretical amount absorbed per day (Qmax):
Qmax (in mg) = Jmax (in mg/cm^2/h) x Surface area of skin contact (in cm^2) x Exposure duration (in h)

(4) Dermal Systemic Exposure = Qmax/BW

A mass balance check was conducted by comparing the Qmax to the total amount of the substance on the skin (Qapp; which is referred to in Table C-2 as the “dermal load”).

(5) For mass balance check:
Qapp = Conc (mg/g) x Product Amount(Amt) x Exposure Frequency (F) X RF
(see individual exposure scenario in Table C-2 for specific values).

If the Qmax > Qapp, then Qapp (equivalent to 100% dermal absorption) was used to characterize the amount absorbed. Otherwise, Qmax was used.

Table C-1. Dermal exposure parameters for maximum flux approach for D3 in face cream (on a ‘day of exposure’ basis)[a]

Substance and sentinel exposure scenario	Age group(s)	Jmax (mg/cm^2/h)	Qmax (mg)
D3, face cream	Adult	0.0233	1.654

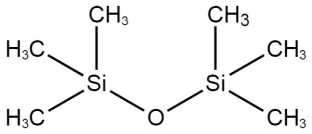
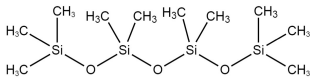
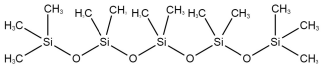
[a] See exposure scenarios in Table C-2 for frequency (F), if relevant.
[b] See Table C-2 for details on the per event and daily exposure scenarios.

Table C-2. Sentinel exposure scenario assumptions

Substance	Sentinel exposure scenario	Assumptions[a]
D3	Face cream	Mass balance check (Qmax/Qapp): 0.0153 Concentration (Conc): 5% = 50 mg/g (MSDS 2010) Age group: Adult Body weight (BW): 70.9 For Estimated Per Event Dermal Exposure: Frequency (F): 1.8 per day (Loretz et al. 2005) Product amount (Amt): 1.2 g/use (Loretz et al. 2005) Surface area of skin contact (SA): 638 cm² (Health Canada 1995) Retention factor (RF): 1 Exposure duration: 24 h/day Qapp - Leave on period: 108 mg Mass balance check (Qmax/Qapp): 0.0153

Appendix D. Hazard summary and read across within the linear siloxanes subgroup

Table D-1. Hazard information for linear siloxanes subgroup

Chemical name	**L2**	**L4**	**L5**
Role	Target substance	Target substance	Target substance
CAS#	107-46-0	141-62-8	141-63-9
Chemical structure			
Vapour pressure (Pa at 25°C)	4451 (at 20°C)	73	7.8
Water solubility (mg/L)	9.3×10^{-1}	6.74×10^{-3}	7.04×10^{-5}
Log K_{oc} (dimensionless)	2.53	5.16	6.3
Toxico-kinetics and metabolism	L2 mostly eliminated via exhalation with < 3% excreted as metabolites in urine; based on oral and inhalation studies in rats (DCC 2008 cited in OECD 2013). Majority of radioactivity eliminated within first 24 hours in a 15-day inhalation study in rats (ECHA 2016).	Read-across from L2 and L5.	25% of single oral gavage dose in rats absorbed in GI tract with 97% of it eliminated in faeces and expired air and < 3% recovered in urine (DCC 1985; ECHA 1985).
Repeat dose toxicity (oral)	NOAEL = 1000 mg/kg bw/day (HTD); 28 day gavage study in rats (Dow Corning cited in OECD 2013).	NOAEL = 25 mg/kg bw/day based on protoporphyrin accumulation in the liver of males at 250 mg/kg bw/day; 28 day	NOAEL = 1000 mg/kg bw/day (HTD); 7- and 28-day gavage study in rats (ECHA 2009c, 2010d).

Chemical name	**L2**	**L4**	**L5**
Role	Target substance	Target substance	Target substance
CAS#	107-46-0	141-62-8	141-63-9
		gavage study in rats (ECHA 2010a). NOAEL = 1000 mg/kg bw/day (HTD); 7- and 28-day gavage study in rats (DCC 2009; ECHA 2010d). LOAEL (OTD) = 500 mg/kg bw/day based on decreased adrenal weights in both sexes and increased thyroid weights in males; 1-year dietary study in rats (DCC 1966a). LOAEL (OTD)= 500 mg/kg bw/day based on heart and kidney effects in females, decreased liver weights and increased spleen weights in males; 8-month dietary study in rabbits (DCC 1966b).	
Repeat dose toxicity (dermal)	NOAEL = 1000 mg/kg bw/day (HTD); rats dosed under occlusion 6 h/day, 5 days/wk for 28 days (DCC 1993b cited in OECD 2013).	Read-across from L2.	Read-across from L2.
Repeat dose toxicity (inhalation)	NOAEC = 6652 mg/m^3 (HTD); 2-wk whole body rat 6 h/day, 5 days/wk (DCC 1992; ECHA 1992).		Read-across from L2.

Chemical name	**L2**	**L4**	**L5**
Role	Target substance	Target substance	Target substance
CAS#	107-46-0	141-62-8	141-63-9
	LOAEC = 950 mg/m^3 based on clinical chemistry changes in females and histopathological changes in the lungs of both sexes; 4-wk nose-only rat 6 h/day, 5 days/wk (DCC 1997c cited in OECD 2013). LOAEC = 140 mg/m^3 based on increased incidence of reduced testes size and/or flaccid testes and histopathological changes in testes in males, histopathological changes in the vagina in females, and histopathological changes in the lungs and kidneys in both sexes; 13-wk nose-only rat 6 h/day, 5 days/wk (DCC 1997b cited in OECD 2013). NOAEC = 33,100 mg/m^3 (HTD); 13-wk whole body rat 6 h/day, 5 days/wk (Caddidy et al. 2001; DCC 1998, 2002 cited in OECD 2013).	NOAEC = 5080 mg/m^3 (HTD); 13-wk whole body rat 5 days/wk (duration of exposure/day not stated) (ECHA 2010b). Read-across from L2.	Read-across from L2.

Chemical name	**L2**	**L4**	**L5**
Role	Target substance	Target substance	Target substance
CAS#	107-46-0	141-62-8	141-63-9
Long-term toxicity (inhalation)	LOAEC = 670 mg/m^3 based on increased incidence of enlarged testes and Leydig cell tumours in males; 2-year whole body rat 6 h/day, 5 days/wk (DCC 2005 cited in OECD 2013).	NR	NR
Reproductive (inhalation)	NOAEC = 2700 mg/m^3 based on liver effects in F1 adults and decreased body weights in F1 and F2 pups at 10,600 mg/m^3; No reproductive effects up to the HTD (33,100 mg/m^3); 2-generation reproductive toxicity study in rats 6 h/day, 7 days/wk, whole body inhalation (WIL Research Laboratories 2006 cited in OECD 2013). NOAEC = 33,100 mg/m^3 (HTD) whole body 1-generation reproductive toxicity study in rats, 6 h/day, 7 days/wk (DCC 1990; WIL Research Laboratories 2000 and Siddiqui et al. 2000 cited in OECD 2013).	LOAEC = 5080 mg/m^3 (OTD) based on failure to deliver litters in 3/10 dams, in absence of other systemic effects in parental animals; 1-generation reproductive toxicity study in rats, 6 h/day, 7 days/wk, whole body inhalation (ECHA 2007a,b).	NR

Chemical name	**L2**	**L4**	**L5**
Role	Target substance	Target substance	Target substance
CAS#	107-46-0	141-62-8	141-63-9
Genetic toxicity	Negative	Negative	Negative
Carcino-genicity (inhalation)	Some evidence of testicular carcinogenicity; 2-year whole body rat 6 h/day, 5 days/wk (DCC 2005 cited in OECD 2013).	NR	NR

Abbreviation: NR = Read-across not required for risk characterization; HTD = highest tested dose; LTD = lowest tested dose; OTD = only tested dose; h = hours, wk = week.