Government of Canada Gouvernement du Canada

Screening Assessment

Ethers Group

Chemical Abstracts Service Registry Numbers
60-29-7
101-84-8
115-10-6
34590-94-8

Environment and Climate Change Canada
Health Canada

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Synopsis

Pursuant to section 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment of four substances referred to collectively under the Chemicals Management Plan as the Ethers Group. Their Chemical Abstracts Service Registry Number (CAS RN[1]), *Domestic Substances List* (DSL) name, common name and abbreviation are listed in the table below.

Substances in the Ethers Group

CAS RN	DSL name	Common name	Abbreviation
60-29-7	Ethane, 1,1'-oxybis-	Diethyl ether	DEE
101-84-8	Benzene, 1,1'-oxybis-	Diphenyl ether	DPE
115-10-6[a]	Methane, oxybis-	Dimethyl ether	DME
34590-94-8	Propanol, 1(or 2)-(2-methoxymethylethoxy)-	Dipropylene glycol methyl ether	DPGME

[a] This substance was not identified under subsection 73(1) of CEPA but was included in this screening assessment as it was considered a priority on the basis of other human health concerns.

DEE, DPE and DME naturally occur at low levels in some foods, but DPGME does not occur naturally in the environment. All four substances in the Ethers Group were included in surveys issued pursuant to section 71 of CEPA. The submitted information indicated that DEE and DPE are not manufactured in Canada above the reporting threshold of 100 kg, while 100 000 kg to 1 000 000 kg of DME and 10 000 kg to 100 000 kg of DPGME were manufactured in Canada in 2011. The four substances were also imported into Canada with quantities ranging from 487 199 kg to 1 287 772 kg. Reported uses are wide-ranging, with most substances being used in air care (for example, air fresheners); automotive, aircraft and transportation (for example, solvents used in the manufacturing of vehicles or functional fluids contained within components of a vehicle); cleaning and furnishing care; fuels and related products; oil and natural gas extraction; and paints and coatings.

In Canada, the substances in the Ethers Group may also be used as components in food packaging materials, food processing aids, food flavouring agents, as medicinal or non-medicinal ingredients in disinfectant, human or veterinary drug products, as non-medicinal ingredients in natural health products, cosmetics, and various other products available to consumers, and as formulants in pest control products.

The ecological risks of the four substances in the Ethers Group were characterized using the ecological risk classification of organic substances (ERC), which is a risk-

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based approach that employs multiple metrics for both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. Hazard profiles are 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 on the basis of their hazard and exposure profiles. Based on the outcome of the ERC analysis, substances in the Ethers Group are considered unlikely to be causing ecological harm.

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to the environment from DEE, DPE, DME and DPGME. It is concluded that DEE, DPE, DME and DPGME 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.

Scenarios that resulted in the highest levels of exposure were used to characterize potential exposure of the general population of Canadians to substances in the Ethers Group through the use of products available to consumers, and from environmental media and food.

According to the available information, the general population is expected to be exposed to DEE from environmental media and from the use of various products available to consumers such as body lotions, corn and callus removers, and automotive starting fluids. Based on laboratory studies, the most critical effects for DEE were maternal toxicity-based changes in body weight and food consumption when laboratory animals were exposed orally, and liver toxicity when they were exposed via the inhalation route.

Exposure of the general population to DPE is expected from environmental media and potential use as a food flavouring agent, and from the use of various products available to consumers such as air fresheners and hand creams. Based on laboratory studies, changes in body weight were noted as the most critical effects for oral and long-term inhalation exposures to DPE.

Exposure of the general population to DME is expected from environmental media and from the use of various products available to consumers such as spray sunscreens. Based on laboratory studies, the critical effect for DME was decreased survival rates in rats exposed long term via inhalation.

Although potential inhalation and dermal exposures to DPGME may occur from the use of products available to consumers, exposure to DPGME is characterized qualitatively as it is considered to be of low hazard potential. DPGME was not identified as inducing

any adverse effects in any of the available studies. A structurally similar substance, propylene glycol methyl ether, was also used to inform the health effects assessment of DPGME.

The human health assessment took into consideration those groups of individuals within the Canadian population who, due to greater susceptibility or greater exposure, may be more vulnerable to experiencing adverse health effects from exposure to substances. The potential for increased susceptibility during development and reproduction was assessed. Exposure estimates are routinely assessed by age to take into consideration physical and behavioural differences during different stages of life. Young children (e.g., 1-year-olds) are expected to have higher exposure to ambient air, household air freshener, and spray sunscreen than adults. All these populations were taken into consideration while assessing the potential harm to human health.

Comparisons of levels of exposure to DEE, DPE and DME from environmental media, and from the use of products available to consumers, as well as exposure to DPE from food from its potential use as a food flavouring agent resulted in margins that are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk. As DPGME is considered to be of low hazard potential, the risk to human health is considered to be low.

On the basis of the information presented in this screening assessment, it is concluded that DEE, DPE, DME and DPGME 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.

It is therefore concluded that DEE, DPE, DME and DPGME do not meet any of the criteria set out in section 64 of CEPA.

Table of contents

List of tables

1. Introduction

Pursuant to section 68 or 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 of four substances referred to collectively under the Chemicals Management Plan as the Ethers Group to determine whether these substances present or may present a risk to the environment or to human health. The substances in this group were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were prioritized through other mechanisms (ECCC, HC [modified 2017]).

The ecological risks of the substances in the Ethers Group were characterized using the ecological risk classification of organic substances (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 on the basis of such factors as 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.

Diethyl ether has been reviewed by the United States Environmental Protection Agency (US EPA) and the German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission). Diphenyl ether has been reviewed by the European Commission (EC), the European Food Safety Agency (EFSA), the Joint (Food and Agricultural Organization/World Health Organization) Expert Committee on Food Additives (JECFA), the MAK Commission and US EPA. Dimethyl ether has been reviewed by the US EPA, MAK Commission and EFSA. Dipropylene glycol methyl ether has been reviewed by the MAK Commission, the Australian Government Department of Health (AGDH) and the Organisation for Economic Co-operation and Development (OECD) Cooperative Chemicals Assessment Programme; an OECD Screening Information Dataset (SIDS) Initial Assessment Report is available. These reviews were used to inform the health effects characterization in this screening assessment.

This 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 September 2019. Empirical data from key studies as well as results from models were used to reach conclusions.

This 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 screening assessment have undergone external review. Comments on

the technical portions relevant to human health were received from Dr. Supratik Kar, Dr. Jerzy Leszczynski and Dr. Ole Jalob Nøstbakken at Risk Sciences International. The ecological portion of this screening 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. Additionally, the draft of this screening assessment (published March 13, 2021) was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of this screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

This 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.[2] This screening assessment presents the critical information and considerations on which the conclusions are based.

2. Identity of substances

The Chemical Abstracts Service Registry Numbers (CAS RNs[3]), *Domestic Substances List* (DSL) names, common names and abbreviations for the individual substances in the Ethers Group are presented in Table 2-1. As part of the categorization exercise, DPGME was considered as a discrete substance under CEPA (ECCC, HC [modified 2017]). However, based on its mixture of isomers with the methyl substituent in either the 1 or 2 position, it is recognized that this substance possesses the characteristics of an unknown or variable composition, complex reaction products or biological materials (UVCB).

[2] 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.

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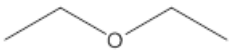
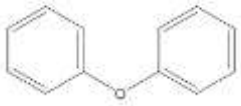
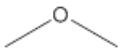
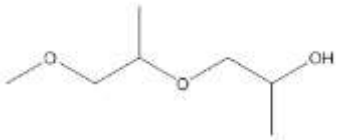
Table 2-1. Substance identities

CAS RN (abbreviation)	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
60-29-7 (DEE)	Ethane, 1,1'-oxybis- (Diethyl ether)	 $C_4H_{10}O$	74.12
101-84-8 (DPE)	Benzene, 1,1'-oxybis- (Diphenyl ether)	 $C_{12}H_{10}O$	170.21
115-10-6 (DME)	Methane, oxybis- (Dimethyl ether)	 C_2H_6O	46.07
34590-94-8 (DPGME[a, b])	Propanol, 1(or 2)-(2-methoxymethylethoxy-) (Dipropylene glycol methyl ether)	 $C_7H_{16}O_3$	148.20

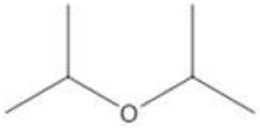
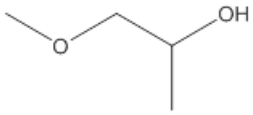
[a] DPGME has characteristics of an UVCB (Unknown or Variable composition, Complex reaction products and/or Biological materials).
[b] The chemical structure of the 1-isomer is shown.

2.1 Selection of analogues and use of (Q)SAR models

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 human health assessment. Analogues were selected that were structurally similar and/or functionally similar (for example, similar physical-chemical properties, toxicokinetics) to substances within this group and that had relevant empirical data that could be used to read across to substances with limited empirical data. The applicability of (Q)SAR models was determined on a case-by-case basis. Details of the read-across data and (Q)SAR models chosen to inform the human health assessment of the Ethers Group are further discussed in the relevant sections of this report.

Information on the identities and chemical structures of the analogues used to inform the human health assessment is presented in Table 2-. Information on the hazard and physical chemical properties of the analogues is presented in Appendix A.

Table 2-2. Analogue identities

CAS RN (abbreviation)	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
108-20-3 (DIPE)	Propane, 2,2'-oxybis- (Diisopropyl ether)	 $C_6H_{14}O$	102.18
1320-67-8 (PGME)	Propanol, 1(or 2)-methoxy- (Propylene glycol methyl ether)	 $C_4H_{10}O_2$	90.12

PGME (CAS RN 1320-67-8) was used as an analogue by the OECD to inform the human health assessment of DPGME, and was considered appropriate based on structural similarities, physical-chemical properties, and toxicokinetics (OECD 2001).

3. Physical and chemical properties

A summary of physical and chemical property data of the substances in the Ethers Group is presented in Table 3-1. When experimental information was limited or not available for a property, (Q)SAR models were used to generate predicted values for the substance. Additional physical and chemical properties are reported in ECCC (2016b).

Table 3-1. Selected experimental physical and chemical property values (at standard temperature) for substances in the Ethers Group

Property	DEE	DPE	DME	DPGME	Reference
Physical state	Liquid	Solid	Gas	Liquid	N/A
Melting point (°C)	-116	27	-142	-83	ChemIDplus 1993-
Vapour pressure (Pa)	7.17×10^4	3.00	5.93×10^5	73.3	ChemIDplus 1993-
Henry's law constant ($Pa \cdot m^3/mol$)	1.25×10^2	28.3	1.01×10^{2} [a]	1.08×10^{-2}[a]	ChemIDplus 1993-
Water solubility (mg/L)	6.04×10^4	18.0	4.60×10^4	1.00×10^6	ChemIDplus 1993-
Log K_{ow} (dimensionless)	0.89	4.21	0.1	-0.35[a]	ChemIDplus 1993-

Abbreviations: N/A, not applicable; K_{ow}, octanol-water partition coefficient

[a] Modelled values

4. Sources and uses

DEE, DME and DPE are reported to naturally occur at low levels in some foods (Nijssen 1963-2018; WHO 2004). DPGME does not occur naturally.

All of the substances in the Ethers Group have been included in surveys issued pursuant to section 71 of CEPA (Canada 2009, 2012). Table 4-1 presents a summary of information reported on the total manufacture and total import quantities for the Ethers Group.

Table 4-1. Summary of information on Canadian manufacturing and imports of substances in the Ethers Group submitted in response to CEPA section 71 surveys

Abbreviation	Total manufacture[a] (kg)	Total imports[a] (kg)	Reporting year	Survey reference
DEE	NR[b]	914 298	2011	Environment Canada 2013
DPE	NR[b]	100 000 – 1 000 000	2008	Environment Canada 2009
DME	100 000 – 1 000 000	487 199	2011	Environment Canada 2013
DPGME	10 000 – 100 000	1 287 772	2011	Environment Canada 2013

Abbreviation: NR, not reported
[a] Values reflect quantities reported in response to CEPA section 71 surveys (Environment Canada 2009, 2013). See surveys for specific inclusions and exclusions (Schedules 2 and 3).
[b] No manufacturing quantities were reported for the substance above the reporting threshold of 100 kg for the specified reporting year.

Error! Reference source not found. presents a summary of the major uses of substances in the Ethers Group according to information submitted in response to CEPA section 71 surveys (Environment Canada 2009, 2013). Table 4-3 presents possible additional uses for substances in the Ethers Group identified in Canada.

Table 4-2. Summary of Canadian uses of substances in the Ethers Group (on the basis of information obtained from CEPA section 71 surveys)

Major uses[a]	DEE	DPE	DME	DPGME
Adhesives and sealants	N	N	Y	N
Air care	N	N	Y	Y
Automotive, aircraft and transportation	N	N	Y	Y
Automotive care	N	N	N	Y
Building or construction materials	N	N	N	Y
Cleaning and furnishing care	N	N	Y	Y
Electrical and electronics	N	N	N	Y
Explosive materials	Y	N	N	N
Fabric, textile and leather articles	N	N	N	Y
Fuels and Related Products, mixtures or manufactured items	Y	N	N	Y
Heat transfer fluid	N	Y	N	N
Ink, toners and colourants	N	N	N	Y
Lubricants and greases	N	N	N	Y
Oil and natural gas extraction	Y	N	N	Y
Paints and coatings	N	N	Y	Y
Personal care	N	N	Y	N
Plastic and rubber materials	N	N	N	Y
Solvent	N	N	N	Y

Abbreviations: Y = this use was reported for this substance; N = this use was not reported for this substance
[a] Non-confidential uses reported in response to CEPA section 71 surveys (Environment Canada 2009, 2013). See surveys for specific inclusions and exclusions (Schedules 2 and 3).

Table 4-3. Possible additional uses in Canada for each of the substances in the Ethers Group

Use	DEE	DPE	DME	DPGME
Food packaging materials[a]	N	N	N	Y[b]
Food processing aids[a]	Y	N	Y	N
Food flavouring agent[a]	N	Y	N	N

Use	DEE	DPE	DME	DPGME
Medicinal or non-medicinal ingredients in disinfectant, human or veterinary drug products[c]	Y	N	Y	Y
Natural Health Products Ingredients Database[d]	Y	Y	Y	Y
Non-medicinal ingredients in natural health products[e]	Y	N	Y	N
Notified to be present in cosmetics under the *Cosmetic Regulations*[f]	Y	Y	Y	Y
Formulant in registered pest control products[g]	N	Y	Y	Y

Abbreviations: Y = use was indicated for this substance; N = use was not indicated for this substance
[a] Personal communications, emails from the Food Directorate (FD), Health Canada, to the Existing Substances Risk Assessment Bureau (ESRAB), Health Canada, dated 2018 and 2019; unreferenced
[b] Used as a solvent in the manufacturing of coatings and printing inks that have no potential for food contact
[c] Personal communication, email from the Therapeutic Products Directorate (TPD), Health Canada, to the ESRAB, Health Canada, dated 2018; unreferenced
[d] NHPID (modified 2022); Personal communications, emails from the Natural and Non-prescription Health Products Directorate (NNHPD), Health Canada, to the ESRAB, Health Canada, dated 2018; unreferenced
[e] LNHPD (modified 2021)
[f] Personal communication, email from the Consumer and Hazardous Products Safety Directorate (CHPSD), Health Canada, to the ESRAB, Health Canada, dated 2018; unreferenced
[g] Personal communication, email from the Pest Management Regulatory Agency, Health Canada, to the ESRAB, Health Canada, dated 2018; unreferenced

In addition to the uses presented above, further uses of substances in the Ethers Group have been identified in Canada. DEE is found in automotive starting fluids (SDS 2017a). DPE is present in air fresheners (SDS 2016a) and a bathroom cleaner (SDS 2017b). DME is used in sealants, spray/marking chalk (SDS 2015a, 2019a), wall repair sprays (SDS 2015a), building insulation foam (SDS 2017d), fabric spray paint (SDS 2018a), tire protectants (SDS 2015b), salt stain removers (SDS 2015c), and deer attractants (SDS 2018b). DPGME is present in a bathroom etching cream (SDS 2016e), leather care product (SDS 2016f), fabric treatment product (SDS 2014a), and pepper spray (SDS 2014b, 2016h).

5. Potential to cause ecological harm

5.1 Characterization of ecological risk

The ecological risks of the substances in the Ethers 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, with 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 (for example, median lethal concentration) 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, from available empirical databases (for example, OECD QSAR Toolbox 2014), from responses to surveys issued pursuant to section 71 of CEPA, or they were generated using (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 (for example, 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. The 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 (that is, 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.

The ERC uses a weighted approach to minimize the potential for both over- and under-classification of hazard and exposure, and of 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 modelled acute toxicity values could result in changes in classification of hazard, particularly metrics relying on tissue residue values (that is, mode of toxic action), many of which are predicted values from (Q)SAR models (OECD QSAR Toolbox 2014). 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 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 thus reflect exposure and risk in Canada on the basis of what is estimated 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 Ethers Group, and the hazard, exposure and risk classification results are presented in ECCC (2016b).

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

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

Substance	ERC hazard classification	ERC exposure classification	ERC risk classification
DEE	low	low	low
DPE	low	low	low
DME	low	high	low
DPGME	low	low	low

On the basis of low hazard and low exposure classifications according to information considered under the ERC, DEE, DPE and DPGME were classified as having a low potential for ecological risk. It is unlikely that these substances are resulting in concerns for the environment in Canada.

According to information considered under the ERC, DME was classified as having a high exposure potential on the basis of a critically long half-life in air and a large annual import quantity according to information submitted in response to a CEPA section 71 survey (Environment Canada 2013). DME was classified as having a low hazard potential and thus a low potential for ecological risk. Although current use patterns result in a high exposure potential, considering its low hazard potential, DME is unlikely to be resulting in concerns for the environment in Canada.

6. Potential to cause harm to human health

6.1 Exposure assessment

Potential exposures to substances in the Ethers Group from environmental media, food, and products available to consumers are presented in this section. For DEE, DPE, and DME, sentinel exposure scenarios resulting in the highest exposures for each age

group are presented to characterize risk. As DPGME is considered to be of low hazard potential (see section 6.2.4), quantitative estimates of exposure to the general population were not derived. Additional details regarding the exposure scenarios are summarized in Appendix B.

6.1.1 Diethyl ether (DEE)

Environmental media and food

DEE has been previously found in the Canadian environment and internationally. Chan et al. (1990) measured DEE in indoor and ambient air in and around 12 Canadian homes. During the initial sampling in 1986, DEE was detected in indoor air samples from 5 of 12 homes with a maximum concentration of 2 µg/m^3, but was not detected in ambient air samples. In the subsequent sampling in 1987, 6 homes were sampled and DEE was detected in one indoor air sample (647 µg/m^3) and in one ambient air sample (24 µg/m^3). In addition to its presence in air, DEE was separately detected in a monitoring well network and outwash aquifer near the Gloucester Landfill in Ontario, with a maximum concentration of 658 µg/L and a detection frequency of 68% (Lesage et al. 1990). In the absence of Canadian monitoring data for soils, level III fugacity modelling was performed using ChemCAN v6.00 (ChemCAN 2003) to simulate environmental partitioning of DEE in Canada. Using the combined reported total manufacture and import quantities (Environment Canada 2013), the predicted concentration of this substance in soil was considered to be negligible. The maximum measured concentrations of DEE in indoor and ambient air around Canadian homes (647 and 24 µg/m^3, respectively) and in a Canadian aquifer (658 µg/L) were used to characterize exposure of Canadians to DEE from environmental media. The highest estimated intake of DEE from environmental media for the Canadian population was 0.44 mg/kg bw/day, corresponding to the intake for 1-year-old children (see Appendix C for details).

Internationally, DEE has been reported in air samples from various locations, including inside cars in Spain, Japan, and Germany (with concentrations up to 25.2 µg/m^3), in indoor air of a multi-storey building after extensive renovations in Germany (with concentrations up to 330 µg/m^3), and in ambient air in Spain (with concentrations up to 0.09 µg/m^3) (Buters et al. 2007; Cadena et al. 2018; Chan et al. 1990; Hippelein 2006; Moreno et al. 2019; Rabaud et al. 2003; Raboni et al. 2015; Ramirez et al. 2010; Smet et al. 1999; Tokumura et al. 2006; Lehtinen and Veijanen 2011). DEE was also detected in water samples from groundwater in Alaska, Colorado, Connecticut, Georgia and Kansas (with concentrations up to 17 µg/L) and at a wetland in Arizona (measured at a concentration of 0.1 µg/L) (Apodaca et al. 2002; Gonthier et al. 2011; Keefe et al. 2004; Lesage et al. 1990; Mullaney et al. 1999; Pope et al. 2002).

No definitive information is available concerning the use of DEE in foods sold in Canada. DEE is known to be used in food processing aids internationally and is potentially used in food processing aids in Canada; if used, dietary exposure to DEE from this use in Canada is expected to be negligible (personal communications, emails

from the FD, Health Canada, to the ESRAB, Health Canada, dated February 2018 and September 2019; unreferenced).

DEE is also reported to occur naturally at low levels in some foods (Nijssen 1963-2018; WHO 2004). The occurrence data used to estimate dietary exposure to DEE was sourced from the Volatile Compounds in Food Database (Nijssen 1963-2018), which reported a concentration of 0.15 ppm in fresh apples and a qualitative presence of DEE in other foods. For each food and beverage category in the database, the highest concentration reported for DEE was conservatively applied to represent the food category (for example, the maximum concentration reported in apples of 0.15 ppm was applied to all apples). Canadian dietary exposure to DEE from its natural occurrence in foods was estimated by multiplying the consumption of foods by the amount of DEE in those foods. Mean and 90th percentile food consumption estimates were based on individual one-day "eaters only" food intakes reported by respondents to the 2004 Canadian Community Health Survey (CCHS) for infants up to 12 months of age[4] and the 2015 CCHS for all other age groups (Statistics Canada 2004, 2015). The mean and 90th percentile dietary exposures estimated in this manner for various age groups are shown in Table 6-1. For some age groups the number of survey respondents was insufficient to generate consumption figures and corresponding exposure estimates (personal communications, emails from the FD, Health Canada, to the ESRAB, Health Canada, dated 2018 and 2019; unreferenced).

Table 6-1. Estimated dietary exposure from the reported natural occurrence levels of DEE in food (µg/kg bw/day)

Parameter	0 – 5 months	6 – 11 months	1 year	2 – 3 years	4 – 8 years	9 – 13 years	14 – 18 years	19+ years
Mean	NA	1.61	1.43	1.43	1.12	0.62	0.44	0.33
90th Percentile	NA	3.86	2.50	2.35	1.97	1.00	0.80	0.57

Abbreviation: NA, not available

The highest estimated intake of DEE as a result of its natural occurrence in food was for 6- to 11- month-olds at 1.61 µg/kg bw/day (mean) or 3.86 µg/kg bw/day (90th percentile). The natural occurrence in food is not further considered, as the potential exposures are lower in comparison to the combined exposures from other environmental media sources.

Products available to consumers

[4] The 2015 CCHS did not include children under 1 year of age.

DEE is present in a starting fluid for combustion engines (SDS 2017a) and self-care products such as body lotion (personal communication, email from the CHPSD, Health Canada, to the ESRAB, Health Canada, dated 2018; unreferenced) and corn and callus remover (personal communications, emails from the NNHPD, Health Canada, to the ESRAB, Health Canada, dated 2018 and 2019; unreferenced). Due to the very high vapour pressure of DEE (7.17×10^4 Pa), exposure to DEE through the use of products available to consumers is expected to be predominantly through the inhalation route; exposure through the oral route is not expected and systemic exposure through the dermal route is expected to be minimal in comparison to inhalation as DEE is not readily absorbed through the skin (MAK Commission 1996). Table 6-2 summarizes the estimated exposures to DEE from the use of these products for the highest exposed age group.

Table 6-2. Estimated inhalation exposures to DEE from the use of products available to consumers

Product scenario (age group)	Product concentration	Inhalation exposure[a] (mg/kg bw(/day))
Body lotion, daily exposure (aged 19 years or above)	3%[b]	0.21
Corn and callus remover, per event exposure (aged 9 to 13 years)	57%[c]	0.078
Starting fluid, per event exposure (aged 19 years or above)	60%[d]	0.63

[a] 100% absorption is assumed for inhalation exposures
[b] Personal communication, email from the CHPSD, Health Canada, to the ESRAB, Health Canada, dated 2018; unreferenced
[c] DailyMed 2019
[d] SDS 2017a

6.1.2 Diphenyl ether (DPE)

Environmental media and food

DPE has been detected in environmental media in Canada and internationally. No measured levels of DPE in Canadian environmental media were identified, although Rogers et al. (1986) conducted a study at the wastewater treatment plant at Iona Island, British Columbia where DPE was identified as a component in base/neutral fractions of wastewater and sludge. Internationally, DPE was measured in indoor air in hair salons in Spain (with concentrations up to 130 µg/m^3) (Ronda et al. 2009) and in water from river basins in the Slovak Republic (with concentrations up to 4.4 µg/L) (Slobodnik et al. 2010).

In the absence of Canadian monitoring data (where DPE was measured), level III fugacity modelling was performed using ChemCAN v6.00 (ChemCAN 2003) to simulate environmental partitioning of DPE in Canada. Using the combined reported total

manufacture and import quantities (Environment Canada 2013), the concentrations in air and water were predicted to be 0.00628 µg/m^3 and 0.0552 µg/L, respectively. These concentrations were used to characterize exposure of Canadians to DPE from environmental media. The predicted concentration of this substance in soil was in the ng/g range and would result in negligible intake.

No definitive information is available concerning the use of DPE in foods sold in Canada. DPE is known to be used as a food flavouring agent internationally and it is possible that this substance is present as a flavouring agent in foods sold in Canada (Burdock 2010). The JECFA evaluated DPE for use as a food flavouring agent (WHO 2004), and estimated the *per capita* intake for the United States (US) population to be 5 µg per person per day (approximately 0.1 µg/kg bw/day) based on annual production volumes reported by the food industry in poundage surveys (NAS 1989, IOFI 1995, Lucas 1999 as cited in WHO 2004). JECFA concluded that this substance presents “no safety concern at current levels of intake when used as a flavoring agent.” In the absence of data on the actual use, if any, of DPE as a flavouring agent in foods sold in Canada, the *per capita* intake estimate for the US population derived by JECFA is an acceptable surrogate for possible Canadian dietary exposure to this substance from its use as a food flavouring agent (personal communications, emails from the FD, Health Canada, to the ESRAB, Health Canada, dated 2018 and 2019; unreferenced).

DPE is also reported to occur naturally at low levels in some foods (Nijssen 1963-2018; WHO 2004). The occurrence data used to estimate dietary exposure to DPE was sourced from the Volatile Compounds in Food Database (Nijssen 1963-2018), which reported a concentration of 0.5 ppm in capers and a qualitative presence of DPE in other foods. For each food and beverage category in the database, the highest concentration reported for DPE was conservatively applied to represent the food category (for example, the maximum concentration reported in capers of 0.5 ppm was applied to all capers). Canadian dietary exposure to DPE from its natural occurrence in foods was estimated with the same method used for DEE (see section 6.1.1). The mean dietary exposure estimated in this manner is 0.061 µg/kg bw/day for Canadians aged 19 years or above; the corresponding 90th percentile dietary exposure cannot be estimated due to a lack of data. For the remaining age groups, the number of survey respondents was insufficient to generate consumption figures and corresponding exposure estimates (personal communications, emails from the FD, Health Canada, to the ESRAB, Health Canada, dated 2018 and 2019; unreferenced). The natural occurrence in food is not further considered in this exposure assessment, as the potential exposures are lower in comparison to potential exposures from food flavouring use as well as the combined exposures from other environmental media sources.

The highest estimated intake of DPE from environmental media and food for the Canadian population was 0.106 µg/kg bw/day, corresponding to the intake for 1-year-old children (see Appendix C for details).

Products available to consumers

DPE is present in various products available to consumers including household air fresheners that can be used indoors (SDS 2016a) and in hand cream (personal communication, email from the CHPSD, Health Canada, to the ESRAB, Health Canada, dated 2018; unreferenced).

Canadians may be exposed to DPE on a daily basis during the use of air fresheners and hand cream. Table 6-3 summarizes the estimated daily inhalation exposure to DPE from the use of these products for the most exposed age group.

Although there is a potential for intermittent exposure to DPE via the dermal and inhalation routes (for example, from the use of bathroom cleaners) and a potential for daily dermal exposure (for example, from the use of hand cream), these exposures were not quantified due to the lack of adverse effects observed in a 13-week dermal study in rats and a 33-day inhalation study in rats (see section 6.2.2 for details).

Table 6-3. Estimated inhalation exposures to DPE from the use of air fresheners and hand cream

Product scenario (age group)	Product concentration	Inhalation exposure[a] (mg/kg bw/day)
Household air fresheners, daily exposure (aged 1 year)	5%[b]	2.3×10^{-2}
Hand cream, daily exposure (aged 19 years or above)	5%[c]	4.5×10^{-2}

[a] 100% absorption is assumed for inhalation exposures
[b] SDS 2016a
[c] Personal communication, email from the CHPSD, Health Canada, to the ESRAB, Health Canada, dated 2018; unreferenced

6.1.3 Dimethyl ether (DME)

Environmental media and food

DME has been reported to the National Pollutant Release Inventory (NPRI). The highest release from a single facility was reported to be 28 tonnes in air emissions in 2017 with releases for this substance identified as fugitive or storage emissions (NPRI 2017). SCREEN3 is a screening-level Gaussian air dispersion model for assessing pollutant concentrations from various sources (SCREEN3 2011). DME emissions were considered to originate from an area source based on facility-specific information. An emission rate of 5.73×10^{-5} g/m^2·s (based on the NPRI air emission data and facility-specific information), receptor height of 1.74 m (Curry et al. 1993), effective emission area of 130 m x 119 m and source height of 6 m (professional judgement), and urban and full meteorology (as a default) were selected. For exposure events happening over the span of a year, it can be expected that the direction of the prevalent winds will be more variable and uncorrelated to the wind direction for a single event; thus, the maximum amortized exposure concentration for one year can be determined by

multiplying the maximum 1-hour exposure by a scaling factor of 0.08 for point source emissions (US EPA 1992). However, such scaling factors are not used for non-point source emissions. To prevent overestimation of the exposures originating from area sources, a scaling factor of 0.2 was used to obtain the yearly amortized concentration from the value of the maximum 1-hour exposure concentration determined by SCREEN3 (2011). This resulted in an estimated concentration of 123 µg/m^3 in ambient air based on the distance (119 m) with the highest calculated concentration.

Internationally, DME was detected in indoor air in Spanish hair salons (with concentrations up to 90 µg/m^3) (Ronda et al. 2009) and in ambient air in Switzerland (with a mean concentration of 0.60 µg/m^3 and a concentration of 1.40 µg/m^3 at the 95th percentile) (Gaeggeler et al. 2008). Pellizzari et al. (1982) also reported the qualitative detection of DME in 1 of 12 breast milk samples in the US.

In the absence of Canadian data on water and soil, level III fugacity modelling was performed using ChemCAN v6.00 (ChemCAN 2003) to simulate environmental partitioning of DME in Canada. Using the combined reported total manufacture and import quantities (Environment Canada 2013), the concentration in water was predicted to be 0.058 µg/L, and the predicted concentration in soil was considered to be negligible.

Concentrations in ambient air from air dispersion model (123 µg/m^3) and in water from fugacity modelling (0.058 µg/L) were used to characterize exposure of Canadians to DME from environmental media. The highest estimated intake of DME from environmental media for the Canadian population was 0.089 mg/kg bw/day, corresponding to the intake for 1-year-old children (see Appendix C).

No definitive information is available concerning the use of DME in foods sold in Canada. DME is known to be used in food processing aids internationally. It is also potentially used in food processing aids in Canada; if used, dietary exposure to DME from this use in Canada is expected to be negligible (personal communications, emails from the FD, Health Canada, to the ESRAB, Health Canada, dated 2018 and 2019; unreferenced).

DME is reported to naturally occur at low levels in some foods such as potatoes and vinegar (Nijssen 1963-2018; WHO 2004) but its presence was not quantified. As such, dietary exposure from its natural occurrence in foods was not estimated in this exposure assessment (personal communications, emails from the FD, Health Canada, to the ESRAB, Health Canada, dated 2018 and 2019; unreferenced).

Products available to consumers

DME is present in aerosol products, including spray chalk paint (SDS 2017c), adhesives (for example, general purpose, temporary for fabric, automotive headliner) (Environment Canada 2013; SDS 2018a), interior wood finish (SDS 2019b), interior wall repair spray (SDS 2015a), foam for building insulation (SDS 2017d), tire protectant (SDS 2015b),

stain remover (SDS 2015c), coating for truck bed liner (SDS 2018d), automotive rust protector (SDS 2017e), fabric paint (SDS 2018b) and jewellery coating (SDS 2016b). DME is also found in self-care products such as hair spray, aerosol temporary hair colour, spray self-tanner (personal communication, email from the CHPSD, Health Canada, to the ESRAB, Health Canada, dated 2018; unreferenced), and spray sunscreen (personal communication, email from the TPD, Health Canada, to the ESRAB, Health Canada, dated 2018; unreferenced). Based on available information, the main function of DME in such products is to act as a propellant.

DME is also an ingredient in spray animal attractant which may be used while in a stand or blind, when stalking deer, on scent trails, in mock scrapes, or when applied to a decoy (SDS 2018c). Exposure to DME during use is expected to be minimal as this product, that is available to consumers, is only used outdoors.

Due to the very high vapour pressure of DME (5.93×10^5 Pa) and its physical state as a gas at room temperature, exposure to DME through the use of products available to consumers is expected to be predominantly through the inhalation route. Exposure through the oral route is not expected, and exposure through the dermal route is expected to be minimal compared to inhalation as DME acts as a propellant and would revert to the gas phase upon discharge from the canister or container. The spray sunscreen scenario represents the highest estimated daily exposure to DME with a concentration in the product of 40% (personal communication, email from the TPD, Health Canada, to the ESRAB, Health Canada, dated 2018; unreferenced) and an estimated inhalation exposure of 1.2 mg/kg bw/day where 100% absorption via the inhalation route is assumed.

6.1.4 Dipropylene glycol methyl ether (DPGME)

As DPGME is considered to be of low hazard potential (see section 6.2.4), quantitative estimates of exposure to the general population were not derived.

Environmental media and food

There were no Canadian environmental monitoring data identified for DPGME. Internationally, DPGME was measured in indoor air of Swedish homes (with concentrations up to 9.16 µg/m^3) and in storage rooms of a German museum (with an average concentration of 12 µg/m^3) (Choi et al. 2010; Schieweck et al. 2005). In addition, DPGME was measured at 0.6 µg/L in treated water from a wastewater treatment plant in France (Bruchet et al. 2007).

Although DPGME may be used as a solvent in the manufacturing of coatings and printing inks used in food packaging materials, these materials have no potential for food contact and exposure to DPGME from food is not expected (personal communications, emails from the FD, Health Canada, to the ESRAB, Health Canada, dated 2018 and 2019; unreferenced).

Products available to consumers

DPGME is present in products available to consumers, including air fresheners (SDS 2015d, 2017f), inks (SDS 2016g), degreasers and disinfectants (MSDS 2010, SDS 2018e), cleaners (SDS 2016c, 2016d, 2015e), rust converters (SDS 2016e), bathroom etching cream (SDS 2016f), paints and coatings (SDS 2015f, 2018f), furniture restorers (SDS 2010), leather care products (SDS 2016g), lubricants (SDS 2015g), automotive products (SDS 2015h), fabric treatment products (SDS 2014a), and pepper spray (SDS 2014b, 2016i). DPGME is also present in various self-care products such as moisturizers and creams, shampoos and conditioners, cleansers, makeup, nail polish, and other hair styling products (personal communication, email from the CHPSD, Health Canada, to the ESRAB, Health Canada, dated February 2018; unreferenced). Potential inhalation and dermal exposures to DGPME may occur during the use of these products.

Consideration of subpopulations who may have greater exposure

There are groups of individuals within the Canadian population who, due to greater exposure, may be more vulnerable to experiencing adverse health effects from exposure to substances. The potential for elevated exposure within the Canadian population was examined. Exposure estimates are routinely assessed by age to take into consideration physical and behavioural differences during different stages of life. In the assessment of background exposure from environmental media, young children (that is, 1-year-olds) had higher exposure to ambient air than adults. In addition, infants also had higher exposure to DPE and DME from household air freshener and spray sunscreen, respectively, as compared to adults.

6.2 Health effects assessment

6.2.1 Diethyl ether (DEE)

DEE has been evaluated internationally by the US EPA (1987, 2009a, 2014) and the German MAK Commission (1996). A REACH dossier is also available (ECHA c2007-2019).

Repeated-dose toxicity

Sprague-Dawley rats (8 for each concentration and sex), ICR mice (24 /sex/dose) and Hartley guinea pigs (8 /sex/dose) were exposed to 1000 or 10 000 ppm (3031 or 30 031 mg/m^3, respectively) DEE for 24 hours/day, for 35 days by whole-body inhalation (US EPA 2009a; MAK Commission 1996). Each exposure group had a concurrent control. No adverse effects were observed in rats. The only treatment-related effects in guinea pigs were a significant decrease in body weight gain and a high mortality rate (25%) in the highest tested group. Due to high mortality, mice and guinea pigs were sacrificed after 20 days of exposure in the high-dose group. Mice were the most sensitive species; at 10 000 ppm, 25% of animals died within 20 days. At 1000 ppm, absolute and relative

liver weights in mice were significantly increased in males (26% and 11%, respectively), and at 10 000 ppm similar but more pronounced changes were observed in males and females (76% and 86% for males, 59% and 66% for females). Degenerative lesions were found in the liver of mice exposed to 10 000 ppm, but not 1000 ppm. No other organs were affected in any of the tested species. Based on these results, No-observed-adverse-effect concentrations (NOAECs) of 10 000 ppm (30 031 mg/m^3) for rats and 1000 ppm (3031 mg/m^3) for guinea pigs, and a lowest-observed-adverse-effect concentration (LOAEC) of 1000 ppm for mice are determined.

In an OECD guideline study, Sprague-Dawley rats (10 /sex/dose) were exposed to DEE 6 hours/day 5 days/week for 13 weeks by flow-past nose-only inhalation route at 0, 500, 1000, or 1500 ppm (0, 1516, 3031, or 4547 mg/m^3, respectively) in a sub-chronic inhalation toxicity study (ECHA c2007-2019). A NOAEC of 1500 ppm (4547 mg/m^3) (highest dose tested) was determined based on the absence of treatment-related effects observed in the study. In a sub-chronic oral study (US EPA 2009a), Sprague-Dawley rats (30/sex/dose) were administered DEE dissolved in corn oil by gavage at 0, 500, 2000 or 3500 mg/kg bw/day for 90 days. Mortalities occurred in the mid- and high-dose groups (7% and 25%, respectively) with discolouration observed in the lung, liver and stomach, as well as alterations in the stomach smooth mucosa. Significantly reduced body weight gains were observed in males of the mid- and high-dose groups, as well as females in the high-dose group. Additional effects in the high-dose group include decreased food consumption, light anaesthesia, decreased absolute weight in brain, heart, kidney, liver, and spleen in males, and increased alanine aminotransferase (ALT) activity and cholesterol levels in both males and females. Considering effects on body weight, hepatic changes and mortality in rats at 2000 mg/kg bw/day, a no-observed-adverse-effect level (NOAEL) of 500 mg/kg bw/day is determined.

Genotoxicity and carcinogenicity

Based on the available information, DEE is not considered genotoxic (MAK Commission 1996; US EPA 2009a).

No carcinogenicity studies for DEE are available. DIPE was used as a supporting chemical in the US EPA Screening Level Hazard Characterization of DEE (US EPA 2014). The US EPA used DIPE repeated-dose, developmental and genotoxicity endpoints to inform the health effects assessment of DEE, but did not use the information on carcinogenicity of DIPE. The US EPA did not derive a carcinogenicity reference dose for DEE based on a lack of suitable data (US EPA 2009a).

Reproductive and developmental toxicity

A number of studies in rats and mice examined the effects of DEE inhalation on foetal development, sperm parameters and male reproductive organs, with conflicting results (MAK Commission 1996). These studies were not conducted according to any established guideline and used concentrations that were close to or greater than

reported inhalation LC_{50} values (95 000 to 220 000 mg/m^3). Thus, the observed effects may be related to hypoxia or maternal stress (MAK Commission 1996).

Two OECD guideline developmental toxicity studies were published in the REACH dossier (ECHA c2007-2019). Wistar rats (24 females/dose with a total of 96 females) were exposed to undiluted DEE by oral gavage at 0, 250, 500, or 1000 mg/kg bw/day, from gestation day (GD) 5 to 19. The NOAEL for maternal toxicity was reported as 500 mg/kg bw/day due to a statistically significant reduction in mean body weight (6.6%), a significant reduction in body weight gain (19.4%) and a significant reduction in food consumption (17.2%) from GD 0-20 at 1000 mg/kg bw/day compared to control animals. The NOAEL for foetal developmental toxicity was reported as 1000 mg/kg bw/day given the absence of any adverse effects noted up to the highest dose tested.

In the second study, New Zealand White rabbits (23 rabbits/group with a total of 92 females) were exposed to undiluted DEE by oral gavage at 0, 80, 140, or 200 mg/kg bw/day, from GD 6 to 28. The NOAEL for maternal toxicity was reported as 80 mg/kg bw/day based on a reduction in mean body weight (3.1% and 4.6%), a reduction in body weight gain (26.5% and 39.1%) and a significant reduction in food consumption (14.3% and 24.4%) for the entire gestation period (GD 0-29) at 140 and 200 mg/kg bw/day, respectively, as compared to the control group. The NOAEL for foetal developmental toxicity was reported as 200 mg/kg bw/day (highest dose tested).

6.2.2 Diphenyl ether (DPE)

Several international agencies have evaluated DPE, including the US EPA (2010, 2017), the EU council (EC 2012), EFSA (2011, 2012), JECFA (WHO 2004) and the German MAK Commission (2004). In addition, a REACH dossier for DPE is available (ECHA c2007-2019).

Repeated-dose toxicity

Several repeated-dose studies in which DPE was administered via the inhalation, dermal or oral route were identified. In some studies, DPE was administered as part of a mixture known as either Therminol A or Dowtherm A, which contains 73.5% DPE and 26.5% diphenyl (CAS RN 92-52-4).

Male rats (20/concentration), male rabbits (4/concentration) and male dogs (2/concentration) were exposed to 0, 35 or 71 mg/m^3 DPE in a whole-body exposure apparatus for 7 hours/day, 5 days/week for 33 days (US EPA 2017). A third group of male and female rats (10/sex) was exposed to 142 mg/m^3 DPE for 27 days. Local irritation of the eye and nose was noted at 71 mg/m^3 but no other treatment-related effects were observed. Based on the lack of adverse effects, a NOAEC of 142 mg/m^3 is determined, which is the highest tested concentration.

In a 13-week dietary study (Johnson et al. 1992; EC 2012), male and female Sprague-Dawley rats (10/sex/dose) were fed 0, 200, 1000 or 5000 ppm of DPE (0, 11.7, 60.7 or

301.1 mg/kg bw/day for males and 0, 14.5, 73.9 or 334.8 mg/kg bw/day for females, respectively). Additional groups of rats (10/sex/dose) were retained for observation during a 4-week recovery period after the 13-week feeding period. Observed health effects included a significant decrease in body weight gain and food consumption at the highest dose tested in males, and at the mid- and high- doses in females. However, as body weights and food consumption were significantly increased in the recovery period, the authors attributed the earlier effects to the unpalatability of the substance in the diet, rather than a treatment-related effect. In consideration of the uncertainty associated with this study, as a result of insufficient reporting, a NOAEL of 15 mg/kg bw/day is determined based on decreased body weight gain in females at 74 mg/kg bw/day.

In a 13-week dermal study (Api and Ford 2003; US EPA 2017), male and female Sprague-Dawley rats (12/sex/dose) were exposed to DPE daily by a semi-occlusive dressing 6 hours/day at 0, 100, 300 or 1000 mg/kg bw/day. No histopathological lesions were observed in any of the examined organs. A significant increase in relative and absolute liver weight was observed in males at 300 mg/kg bw/day; however, this was not a dose-dependent effect. At 1000 mg/kg bw/day, significantly higher relative brain, kidney and liver weights were observed. A reduction in body weight gain in males was observed. In females, relative liver weights were significantly increased at 300 mg/kg bw/day, and both relative and absolute liver weights were increased in the highest dose tested. Considering the absence of histopathological effects of the affected organs, the lack of significant changes in blood or urine parameters, and the lack of dose-response relationships, the study authors concluded that DPE did not induce any adverse systemic effects and considered the organ weight changes to lack of biological significance. Thus, the NOAEL is set at 1000 mg/kg bw/day, which is the highest dose tested.

A mixture of Therminol A (73.5% DPE) was administered by whole-body inhalation to Sprague-Dawley rats (25/sex/dose) as an aerosol at concentrations of 0, 7.4, 37.5 or 95.6 mg/m^3 DPE for 6 hours/day, 5 days/week for 7 or 14 weeks (US EPA 2017). In animals exposed for 14 weeks, significantly reduced body weight gains in males and females were observed at 95.6 mg/m^3 DPE in weeks 2-6. There were reduced white blood cell counts for males in the low- and mid-concentration groups, but the effect was not dose-dependent. In addition, significantly lower relative weight of liver (in males and females), brain and spleen (in females) were observed in the highest concentration group, but these may be attributed to increased absolute organ weights and reduced body weights. The authors assigned a NOAEC of 37.5 mg/m^3 DPE based on body weight changes at 95.6 mg/m^3 DPE.

Genotoxicity and carcinogenicity

DPE is not considered genotoxic as demonstrated by several *in vitro* and *in vivo* assays (US EPA 2017).

In a 13-month carcinogenicity study, male albino rats (8 animals/dose) were given diets containing DPE at 530 mg/kg bw/day, or as a mixture of Therminol A (73.5% DPE) at

396 mg/kg bw/day DPE. No tumours or treatment-related pathological effects were observed in animals treated with DPE alone, or as a mixture (WHO 2004).

Reproductive and developmental toxicity

In a rat dietary repeated-dose study, the reproductive organs of both genders were examined macroscopically and histopathologically; no adverse effects related to treatment were found (Johnson et al. 1992; EC 2012).

There are no reproductive or developmental toxicity studies for DPE available where DPE is not part of a mixture.

In a developmental toxicity study (US EPA 2017; ECHA c2007-2019), a mixture of Therminol A containing 73.5% DPE was given in corn oil to pregnant Sprague-Dawley rats (24 animals/dose) by gavage at 0, 36.75, 147 or 367.5 mg/kg bw/day DPE between GD 6-15. Animals were sacrificed on GD 20 and both the dams and foetuses were examined for clinical and developmental toxicity. At 147 mg/kg bw/day DPE, significant reduction in body weight gain (20% less than control) and food consumption were noted, along with salivation and staining of the ano-genital area. These effects were more severe at the highest dose tested, where two dams died. In the foetuses, no overt toxicity was observed at any of the tested doses, including any skeletal, soft-tissue or external malformations. Thus, the NOAEL for maternal toxicity is 36.75 mg/kg bw/day DPE based on body weight changes at 147 mg/kg bw/day DPE. The NOAEL for developmental toxicity is 367.5 mg/kg bw/day DPE, which is the highest dose tested.

6.2.3 Dimethyl ether (DME)

Several international agencies have evaluated DME, including the US EPA (2009b), EFSA (2009, 2015) and the German MAK Commission (1990). In addition, a REACH dossier for DME is available (ECHA c2007-2019). In an Initial Risk-Based Prioritization of High Production Volume Chemicals Report, the US EPA recommended that DME be classified as low priority based on its low human health hazard (US EPA 2009b).

Repeated-dose toxicity

As DME is a gas at body temperature, animals were exposed to the substance via inhalation in all available repeated-dose toxicity studies.

No critical health effects via inhalation were identified in two short-term studies and one sub-chronic study in rats at concentrations up to 94 211 mg/m^3 DME (MAK Commission 1990). In a chronic study (MAK Commission 1990), male and female Wistar rats (25/sex/dose) were exposed to DME at 0, 197, 1964 or 18 830 ppm (0, 371, 3701 or 35 480 mg/m^3, respectively) for 6 hours/day, 5 days/week for 30 weeks. No effects were noted on body weight, food consumption, clinical signs or the eye. No abnormalities in the haematology or urinalysis were observed except for a significantly higher level of aspartate aminotransferase activity in males exposed to 1964 ppm only and in alanine

aminotransferase (ALT) activity in both males and females exposed to 18 830 ppm. In addition, there was a significant reduction in relative liver weight (8% less than control) in males of the highest tested concentration.

In a 2-year carcinogenicity good laboratory practices study (MAK Commission 1990), male and female Crl:CD rats (100/sex/dose) were exposed to DME vapour at 0, 2000, 10 000 or 25 000 ppm (0, 3768, 18 842 or 47 105 mg/m^3, respectively) for 6 hours/day, 5 days/week for 104 weeks. The most notable findings were a significant increase in body weight and an increase in mortality of male rats at the mid- and high-concentration groups at the end of the study period. In the highest concentration group, males showed a decrease in erythrocyte count, an increase in spleen weight and evidence of splenic congestion at 6 months, along with normal bone histology. In the same group, females showed a decrease in erythrocyte counts at 3 months. These changes, however, were not noted at later time-points. Aside from observations made in the spleen, no histopathological effects were observed in other organs. The total number of rats with at least one observable mass (benign or malignant) was used for comparison. The number of observed masses in female rats was statistically higher in the highest dose group compared to control, including the presence of mammary tumours. However, the study authors did not consider this effect to be treatment-related as the incidence of masses and tumours in the control group were low compared to historical data. Thus, a NOAEC of 2000 ppm (3768 mg/m^3) is determined based on reduced survival rate in male rats at the mid and high concentrations.

Genotoxicity and carcinogenicity

DME is not considered genotoxic as demonstrated in several *in vitro* assays (MAK Commission 1990; US EPA 2009b; ECHA c2007-2019).

In the previously described 2-year carcinogenicity study in rats (MAK Commission 1990), it was considered that DME did not induce a carcinogenic effect.

Reproductive and developmental toxicity

No reproductive toxicity studies are available for DME. However, no adverse effects were observed in gross and histopathological examination of male and female reproductive organs in several short-term and long-term repeated exposure inhalation studies in rats and hamsters.

Two developmental studies for DME conducted in rats are available (CIVO Institute 1981; Haskell Labs 1983; US EPA 2009b; MAK Commission 1990), where pregnant Wistar and Crl:CD rats were exposed to DME up to 28 000 ppm (52 758 mg/m^3) for 6 hours/day from GD 6 to 16. No maternal toxicity was observed in any of the treatment groups. No treatment-related soft-tissue malformations were observed in the foetuses of all treatment groups. The incidence of supernumerary lumbar ribs (both uni- and bi-lateral) was significantly higher in the treatment groups compared to the controls, but the biological significance of this finding was considered uncertain by study reviewers

(Haskell Labs 1983; MAK Commission 1990). Significant differences in the ossification of hind limb phalanges as well as cervical and thoracic vertebrae were also observed. However, the study authors and reviewers considered these differences not to be treatment-related due to the lack of a clear concentration-response relationship, and attributed them to normal variation in ossification of this animal strain (MAK Commission 1990).

6.2.4 Dipropylene glycol methyl ether (DPGME)

DPGME has been evaluated internationally by the OECD (2001) and the German MAK Commission (1993). Reviews by ECETOC (Gribble 2005) and the Cosmetic Ingredient Review (Robinson et al. 2009) on the health effects of glycol ethers, including DPGME, are also available. In addition, a REACH dossier for DPGME exists (ECHA c2007-2019). In a SIDS Initial Assessment Meeting, the OECD recommended that DPGME be classified as low priority for risk evaluation based on its low hazard profile (OECD 2001). Similarly, in a multi-chemical Tier I human health risk assessment carried out by the AGDH (2018), DPGME was listed as one of the chemicals that were not considered to pose an unreasonable risk to the health of workers or the general public.

Repeated-dose toxicity

Oral, dermal and inhalation repeated-dose studies are available for DPGME.

In eight separate inhalation studies, mice, rats, rabbits, guinea pigs and monkeys exposed to DPGME concentrations up to 300 ppm (1818 mg/m^3) for 6-7 hours/day for 2 to 31 weeks did not experience any adverse effects (OECD 2001). It should be noted that 300 ppm is the highest concentration attainable of DPGME vapour at standard temperature and pressure.

In an oral short-term study (OECD 2001), Sprague-Dawley rats (5/sex/dose) were given 0, 40, 200 or 1000 mg/kg bw/day DPGME by gavage for 28 days. The NOAEL is set at 1000 mg/kg bw/day due to the lack of biologically significant effects at the highest dose tested.

No adverse effects were observed in male Wistar rats (8/dose) exposed to 0, 100 or 1000 mg/kg bw/day DPGME dermally by occlusive and semi-occlusive applications for 4 hours/day, 5 days/week for four weeks (OECD 2001). In a semi-occlusive dermal study, male rabbits (5-7/dose) were exposed to 0, 950, 2850, 4750, or 9510 mg/kg bw/day DPGME for 5 days/week for 90 days (OECD 2001). Minor skin irritation, narcosis and some deaths were observed in animals exposed to 4750 mg/kg bw/day and above. Thus, the NOAEL is 2850 mg/kg bw/day.

Genotoxicity and carcinogenicity

DPGME is not considered to be genotoxic as demonstrated by several *in vitro* assays (OECD 2001).

No carcinogenicity studies for DPGME are available. However, sub-chronic and chronic studies on rats, rabbits, guinea pigs and monkeys did not report any significant tumour incidence when 300 ppm (the maximum attainable concentration) DPGME was administered by inhalation for 7 hours/day, 5 days/week up to 31 weeks (OECD 2001).

The OECD (2001) used a supporting chemical, PGME, to evaluate the carcinogenic potential of DPGME using a 2-year inhalation study conducted in Fischer rats and B6C3F1 mice which were exposed to 0, 300, 1000 or 3000 ppm (0, 1106, 3686 or 11 058 mg/m^3, respectively) of PGME for 6 hours/day, 5 days a week (OECD 2001). No evidence of carcinogenicity was observed in either species up to the highest tested concentration.

Reproductive and developmental toxicity

No reproductive toxicity studies are available for DPGME. However, no gross or histopathological effects were observed in the testes or ovaries of male and female rats and rabbits exposed to DPGME for 90 days by inhalation (OECD 2001).

No maternal or foetal toxicity was observed in two studies where pregnant Fischer 344 rats and New Zealand rabbits were exposed up to 300 ppm DPGME by whole-body inhalation from GD 6-15 (rats) and GD 7-19 (rabbits) for 6 hours/day (OECD 2001).

Consideration of subpopulations who may have greater susceptibility

There are groups of individuals within the Canadian population who, due to greater susceptibility, may be more vulnerable to experiencing adverse health effects from exposure to substances. The potential for susceptibility during different life stages or by sex are considered from available studies. Studies in the hazard database examined differences between the sexes. In this assessment, studies considered include experimental animal studies that examined reproductive and developmental effects in the young, and toxicity to pregnant animals. A maternal toxicity endpoint was used as one of the critical health effects to characterize risk from exposure to DEE.

6.3 Characterization of risk to human health

Table 6- to 6-6 provide relevant exposure and hazard values for DEE, DPE and DME, as well as resultant margins of exposure (MOEs), for determination of risk.

6.3.1 Diethyl ether (DEE)

A NOAEL of 80 mg/kg bw/day, based on reduced body weight, body weight gain, and food consumption in pregnant rats in a developmental oral gavage study (ECHA c2007-2019), was considered to be the most relevant endpoint for oral and inhalation exposures of DEE from environmental media.

A LOAEC of 3031 mg/m^3 ($LOAEL_{adj}$ = 4256 mg/kg bw/day) was considered the most relevant endpoint for exposure to products available to consumers via inhalation, based on increased liver weights at 3031 mg/m^3 DEE and increased liver degeneration and mortality at 30 031 mg/m^3 DEE in mice exposed via inhalation for up to 35 days (US EPA 2009a). The mouse was the most sensitive species tested in this study (compared to the rat and guinea pig) and all animals were exposed continuously for up to 35 days. Exposure from the use of DEE in body lotion is expected to be predominately from the inhalation route mainly due to the high vapour pressure of DEE, thus a comparison to the 35-day inhalation study was considered appropriate.

On the basis of the conservative parameters used in estimating exposure, the resulting MOEs for the oral and inhalation routes are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk of DEE.

Table 6-4. Relevant exposure and hazard values for DEE, as well as margins of exposure, for determination of risk

Exposure scenario	Systemic exposure (mg/kg bw/day)[a]	Critical effect level (mg/kg bw/day)	Critical health effect endpoint	MOE[f]
Environmental media, daily exposure (aged 1 year) [e]	0.44 [b]	NOAEL = 80 (developmental oral gavage study in rabbits)	Maternal toxicity based on decreases in body weight, body weight gain and food consumption	182
Body lotion, daily exposure (aged 19 years or above)	0.21 [c]	$LOAEL_{adj}$ = 4256[d] (35-day inhalation study in mice)	Liver toxicity in mice at adjusted dose of 4256 mg/kg bw/day[d]	20 267
Corn and callus remover, per event exposure (aged 9 to 13 years)	7.8×10^{-2} [c]	$LOAEL_{adj}$ = 4256[d] (35-day inhalation study in mice)	Liver toxicity in mice at adjusted dose of 4256 mg/kg bw/day[d]	54 564
Starting fluid, per event exposure (aged 19 years or above)	0.63 [c]	$LOAEL_{adj}$ = 4256[d] (35-day inhalation study in mice)	Liver toxicity in mice at adjusted dose of 4256 mg/kg bw/day[d]	6756

Abbreviations: MOE, margin of exposure; NOAEL, no-observed-adverse-effect level; $LOAEL_{adj}$, adjusted lowest-observed-adverse-effect level

[a] Systemic exposure is derived from the "external dose on day of exposure" calculated using ConsExpo Web (2016), conservatively assuming 100% absorption for inhalation exposures. This value represents the sum of external doses for multiple events that take place on the same day, where applicable. See Appendix C for more details.

[b] Represents the sum of oral and inhalation exposures.

[c] Represents inhalation exposure.

[d] Critical effect levels are calculated based on converting NOAECs or LOAECs from inhalation toxicity studies into internal doses that account for animal inhalation rate (m^3/day), body weight (kg), and time adjustment factors (hours

of exposure/24; days of exposure in a week/7), unless specified otherwise. Animal inhalation rates were determined using the equation provided in Bide et al. (2000). Animal body weights were derived from the study reports if available; a default value as presented in Meek et al. (1994) was used otherwise.
[e] Dietary exposure to DEE from use in Canada as food processing aids is expected to be negligible. The natural occurrence in food is not further considered as the potential exposures are lower in comparison to the combined exposures from other environmental media sources.
[f] Target MOE=100 (x10 for inter-species variation; x10 for intra-species variation)

6.3.2 Diphenyl ether (DPE)

A NOAEL of 15 mg/kg bw/day, based on changes in body weight gain in female rats exposed to 74 mg/kg bw/day DPE in the diet for 13 weeks (Johnson et al. 1992; EC 2012), was considered the most relevant endpoint for oral exposure. Reduced food consumption due to palatability issues with the substance was possibly a contributing factor to the reduced body weight gains observed; however, limited information is available to validate this assumption. In addition, similar effects were observed in pregnant rats exposed to a mixture containing DPE by oral gavage, where significant body weight gain reductions occurred starting from 147 mg/kg bw/day DPE. Thus, a NOAEL of 15 mg/kg bw/day is considered appropriate and would be protective of any potential body weight effects that could occur at higher doses.

A NOAEC of 37.5 mg/m^3 DPE ($NOAEL_{adj}$ = 6 mg/kg bw/day) based on body weight changes in rats exposed via inhalation to 95.6 mg/m^3 DPE for 6 hours/day, 5 days/week for 13-14 weeks (US EPA 2017), was considered the most relevant endpoint for long-term inhalation exposure. This study was considered appropriate to characterize the risk from exposure from hand cream as the most likely route of exposure for this substance would be via inhalation due to its moderate vapour pressure and low dermal absorption rate (approximately 20% of 1000 mg/kg bw/day of DPE was absorbed in rats over a 72-hour period as described in Api and Ford 2003; US EPA 2017), and lack of adverse effects in rats when DPE was administered dermally up to 1000 mg/kg bw/day for 13 weeks.

For characterizing the risk from dermal and short-term inhalation exposures, it was further considered that there was a lack of adverse effects in rats when DPE was administered dermally up to 1000 mg/kg bw/day for 13 weeks, and that there was also a lack of adverse effects by inhalation up to the highest tested concentration of 142 mg/m^3 for 27 days. As such, MOEs for dermal and short-term inhalation exposures were not derived and the risk to human health from relevant scenarios is considered to be low.

As such, the resulting MOEs (Table 6-5) for the oral and long-term inhalation exposure scenarios are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk of DPE.

Table 6-5. Relevant exposure and hazard values for DPE, as well as margins of exposure, for determination of risk

Exposure scenario	Systemic exposure (mg/kg bw/day)[a]	Critical effect level (mg/kg bw/day)	Critical health effect endpoint	MOE[e]
Environmental media and food, daily exposure (aged 1 year)	1.1×10^{-4} [b]	NOAEL = 15 (13-week diet study in rats)	Changes in body weight gain in female rats at 74 mg/kg bw/day	136 000
Household air freshener, daily exposure (aged 1 year)	2.3×10^{-2} [c]	$NOAEL_{adj}$ = 6[d] (14-week inhalation study in rats)	Changes in body weight gain in rats at adjusted dose of 15 mg/kg bw/day[d]	261
Hand cream, daily exposure (aged 19 years or above)	4.5×10^{-2} [c]	$NOAEL_{adj}$ = 6[d] (14-week inhalation study in rats)	Changes in body weight gain in rats at adjusted dose of 15 mg/kg bw/day[d]	133

Abbreviations: MOE, margin of exposure; $NOAEL_{adj}$, adjusted no-observed-adverse-effect level
[a] Systemic exposure is derived from the "external dose on day of exposure" calculated using ConsExpo Web (2016), conservatively assuming 100% absorption for inhalation exposures. This value represents the sum of external doses for multiple events that take place on the same day, where applicable. See Appendix C for more details.
[b] Represents the sum of oral and inhalation exposures.
[c] Represents inhalation exposure.
[d] Critical effect levels are calculated based on converting NOAECs or LOAECs from inhalation toxicity studies into internal doses that account for animal inhalation rate (m^3/day), body weight (kg), and time adjustment factors (hours of exposure/24; days of exposure in a week/7), unless specified otherwise. Animal inhalation rates were determined using the equation provided in Bide et al. (2000). Animal body weights were derived from the study reports if available; a default value as presented in Meek et al. (1994) was used otherwise.
[e] Target MOE=100 (x10 for inter-species variation x x10 for intra-species variation)

6.3.3 Dimethyl ether (DME)

A NOAEC of 3768 mg/m^3 ($NOAEC_{adj}$ = 590 mg/kg bw/day) based on decreased survival rates in male rats exposed to 18 842 or 47 105 mg/m^3 DME via inhalation for 6 hours/day, 5 days/week for 2 years (MAK Commission 1990) was selected as the most relevant endpoint for long-term inhalation exposures. The resulting MOEs are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk of DME.

For short-term inhalation exposures, it was considered that there was a lack of adverse effects in rats exposed to DME for 10 days up to 94 211 mg/m^3; as such, MOEs for short-term inhalation exposures were not derived and the risk to human health from relevant scenarios is considered to be low.

Table 6-6. Relevant exposure and hazard values for DME, as well as margins of exposure, for determination of risk

Exposure scenario	Systemic exposure (mg/kg bw(/day))[a]	Critical effect level (mg/kg bw/day)	Critical health effect endpoint	MOE[e]
Environmental media, daily exposure (aged 1 year)	8.9×10^{-2} [b]	$NOAEL_{adj}$ = 590[d] (2-year inhalation study in rats)	Reduced survival rates in male rats at adjusted dose of 2955 mg/kg bw/day[d]	6600
Spray sunscreen, daily exposure (aged 1 year)	1.2[c]	$NOAEL_{adj}$ = 590[d] (2-year inhalation study in rats)	Reduced survival rates in male rats at adjusted dose of 2955 mg/kg bw/day[d]	492

Abbreviations: MOE, margin of exposure; $NOAEL_{adj}$, adjusted no-observed-adverse-effect level
[a] Systemic exposure is derived from the "external dose on day of exposure" calculated using ConsExpo Web (2016), conservatively assuming 100% absorption for inhalation exposures. This value represents the sum of external doses for multiple events that take place on the same day, where applicable. See Appendix C for more details.
[b] Represents the sum of oral and inhalation exposures.
[c] Represents inhalation exposure.
[d] Critical effect levels are calculated based on converting NOAECs or LOAECs from inhalation toxicity studies into internal doses that account for animal inhalation rate (m^3/day), body weight (kg), and time adjustment factors (hours of exposure/24; days of exposure in a week/7), unless specified otherwise. Animal inhalation rates were determined using the equation provided in Bide et al. (2000). Animal body weights were derived from the study reports if available; a default value as presented in Meek et al. (1994) was used otherwise.
[e] Target MOE=100 (x10 for inter-species variation x x10 for intra-species variation)

6.3.4 Dipropylene glycol methyl ether (DPGME)

DPGME is considered to have a low hazard potential given that no adverse effects were observed as a result of oral or dermal exposures up to the limit dose, or inhalation exposures up to the maximum concentration attainable, and given the available information indicating a low concern for reproductive, developmental or genotoxic effects. In addition, based on read-across from the carcinogenicity endpoint of the analogue PGME, DPGME is not likely to be carcinogenic. As such, exposure estimates were not derived and the risk to human health is considered to be low.

6.4 Uncertainties in evaluation of risk to human health

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

Table 6-7. Sources of uncertainty in the risk characterization

Key source of uncertainty	Impact
There is a lack of Canadian monitoring data for substances in the Ethers Group in environmental media (for example, air and water).	+/-

Key source of uncertainty	Impact
There is a lack of carcinogenicity, reproductive toxicity and long-term repeated-dose studies for DEE.	+/-
The use of a eutectic mixture (Therminol A) in some DPE hazard studies results in uncertainty in determining the component causing the observed health effects.	+/-
There is uncertainty in the relevance of changes to body weight and food consumption observed in the developmental rabbit study used for risk characterization of DEE. In the absence of additional data to account for these changes, they were considered treatment-related.	+

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

7. Conclusion

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to the environment from DEE, DPE, DME and DPGME. It is concluded that DEE, DPE, DME and DPGME 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.

Considering all the information presented in this screening assessment, it is concluded that DEE, DPE, DME and DPGME 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.

It is therefore concluded that DEE, DPE, DME and DPGME do not meet any of the criteria set out in section 64 of CEPA.

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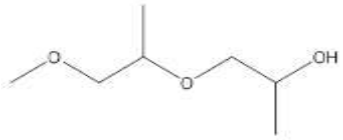
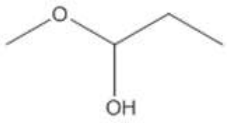
Appendix A. Summary table of read-across for health effects endpoints

Table A-1. Summary table of physical-chemical properties and health effects for DPGME and PGME

Property	DPGME (target)	PGME (analogue)
Structure		
Physical state	Liquid	Liquid
Melting point (°C)	–83[b]	-95[c]
Vapour pressure (Pa)	7.33×10^{1} [b]	1.2[c]
Henry's law constant ($Pa \cdot m^3/mol$)	1.08×10^{-2} [a]	9.3×10^{-2} [c]
Water solubility (mg/L)	1.00×10^{6} [b]	1.00×10^{5} [c]
Log K_{ow} (dimensionless)	–0.35[a]	-0.49[c]
Genotoxicity	Negative	N/A
Short-term oral	NOAEL = 1000 mg/kg bw/day (28-day oral study in rats; no adverse effects)	N/A
Short-term inhalation	NOAEC = 1818 mg/m^3 (2-week studies in rats, mice; no adverse effects)	N/A
Short-term dermal	NOAEL = 1000 mg/kg bw/day (4-week study in rats; no adverse effects)	N/A
Sub-chronic oral	NA	N/A
Sub-chronic inhalation	NOAEC = 1818 mg/m^3 (13-week studies in rats, rabbits; no adverse effects)	N/A
Sub-chronic dermal	NOAEL = 2850 mg/kg bw/day (90-day study in rabbits; minor skin irritation, narcosis & death)	N/A
Chronic oral	NA	N/A

Property	DPGME (target)	PGME (analogue)
Chronic inhalation	NOAEC = 1818 mg/m^3 (31-week studies in rats, rabbits, guinea pigs, monkeys; no adverse effects)	N/A
Chronic dermal	NA	N/A
Carcinogenicity	NOAEC = 11 058 mg/m^3 (read-across from PGME)	NOAEC = 11 058 mg/m^3 (2-year inhalation carcinogenicity study in rats, mice; no carcinogenic effects)
Reproductive and/or developmental toxicity	NOAEC = 1818 mg/m^3 (developmental inhalation studies in rats, rabbits; no adverse foetal effects)	N/A

Abbreviations: N/A, not applicable; NA, not available
[a] Modelled values
[b] ChemIDplus 1993-
[c] PubChem 2004-

Appendix B. Parameters used to estimate human exposure to DEE, DPE and DME from the use products available to consumers

Human exposure estimates from the use of products available to consumers were estimated using ConsExpo Web (ConsExpo Web 2016). Unless otherwise specified in the exposure scenarios below, default parameters from the ConsExpo Web model were used. Default parameters were selected from the General Fact Sheet (RIVM 2014), Cleaning Product Fact Sheet (RIVM 2018) and ConsExpo spray model documentation (RIVM 2009) and the Cosmetics Fact Sheet (RIVM 2006). To be conservative, absorption from the inhalation route was assumed to be 100% for DEE, DPE and DME, and absorption from the dermal route was assumed to be 100% for DPE.

Inhalation rates and body weights of the users are specified in Health Canada (2015a) and are summarized in Table A-1.

Table B-1. Human inhalation rates and body weights for various age groups (Health Canada 2015)

Age group	Inhalation rate (m^3/day)	Body weight (kg)
19 years or above	15.1	74
14 to 18 years	15.9	62
9 to 13 years	13.9	42
4 to 8 years	11.1	23
2 to 3 years	9.2	15
1 year	8.0	11

Table B-2. Human exposure parameters and assumptions for products available to consumers containing DEE

Exposure scenario, route of exposure and age group	Parameters used in ConsExpo Web
Body lotion (daily exposure), inhalation, aged 19 years or above[a]	Model: Exposure to vapour – instantaneous release Use frequency: 1/day (Ficheux et al. 2015; Wu 2010) Exposure duration: 24 hours (RIVM 2006) Product amount: 10 g (Ficheux et al. 2016) Weight fraction: 0.03 (personal communication, email from the CHPSD, Health Canada, to the ESRAB, Health Canada, dated February 2018; unreferenced) Room volume: 20 m^3 (ConsExpo Web 2016) Ventilation rate: 0.6/h (ConsExpo Web 2016)
Corn and callus remover (per event exposure), inhalation, aged 9 to 13 years	Model: Exposure to vapour – instantaneous release Exposure duration: 10 minutes (professional judgement) Product amount: 0.7 g (as per use instructions in Health Canada's Licensed Natural Health Products Database, corresponds to 2 drops of 0.5 mL each with a density of 0.7 g/mL for DEE) Weight fraction: 0.57 (DailyMed 2019) Room volume: 10 m^3 (default for bathroom, RIVM 2014) Ventilation rate: 2.0/h (default for bathroom, RIVM 2014)
Starting fluid (per event exposure), inhalation, aged 19 years or above	Model: Exposure to vapour – instantaneous release Exposure duration: 30 minutes (professional judgement) Product amount: 12 g (assumed 5 sprays of 2 seconds each based on instructions for a similar

Exposure scenario, route of exposure and age group	Parameters used in ConsExpo Web
	product, with a mass generation rate of 1.2 g/s (RIVM 2009)) Weight fraction: 0.6 (SDS 2017c) Room volume: 34 m^3 (default for garage, RIVM 2014) Ventilation rate: 1.5/h (default for garage, RIVM 2014)

[a] The age group of 19 years and above was selected as the corresponding product is expected to be used by adults only. Younger age groups were considered for other similar products which resulted in lower exposures on a per kg basis.

Table B-3. Human exposure parameters and assumptions for products available to consumers containing DPE

Exposure scenario, route of exposure and age group	Parameters used in ConsExpo Web
Household air freshener (daily exposure), inhalation, aged 1 year	Model: Exposure to vapour – instantaneous release Exposure duration: 24 hours (professional judgement) Product amount: 0.18 g (package indicates that 5.5 mL lasts 30 days, assumed a density of 1 g/mL (US EPA 2016)) Weight fraction: 0.05 (SDS 2016a) Room volume: 20 m^3 (default for unspecified room, RIVM 2014) Ventilation rate: 0.6/h (default for unspecified room, RIVM 2014)

Hand cream (daily exposure), inhalation, aged 19 years or above	Model: Exposure to vapour – evaporation model, constant release area Exposure duration: 24 hours (professional judgement) Use frequency: 1/day (adjustments made to the product amount to account for the conservative estimate that the exposure duration is for 24 hours; Ficheux et al. 2015) Product amount: 3.2 g (as the product amount for one application is 1.6 g and hand cream is estimated to be used twice a day, surface area adjustment based on data in Ficheux et al. 2016) Weight fraction: 0.05 (personal communication, email from the CHPSD, Health Canada, to the ESRAB, Health Canada, dated 2018; unreferenced) Release area: 910 cm^2 (equivalent to the surface area of 2 hands) Room volume: 58 m^3 (default for living room; expected to be representative of mixing in indoor air over the day, RIVM 2014) Ventilation rate: 0.5/h (default for living room, RIVM 2014) Application temperature: 32°C Molecular weight matrix: 1000 g/mol

Table B-4. Human exposure parameters and assumptions for products available to consumers containing DME

Exposure scenario, route of exposure and age group	Parameters used in ConsExpo Web
Spray sunscreen (daily exposure), inhalation, aged 1 year	Model: Exposure to vapour – evaporation model, constant release area Use frequency: 1.6/day (Ficheux et al. 2015) Exposure duration: 20 minutes (professional judgement) Product amount: 2.5 g (Ficheux et al. 2016) Weight fraction: 0.4 (personal communication, email from the TPD, Health Canada, to the ESRAB, Health Canada, dated 2018; unreferenced) Release area: 2505 cm^2 (equivalent to the surface area of ¾ legs, hands, ½ feet, face and neck) Room volume: 10 m^3 (default for bathroom, RIVM 2014) Ventilation rate: 2/h (default for bathroom, RIVM 2014) Application temperature: 32°C Molecular weight matrix: 1000 g/mol

Appendix C. Estimates of human daily intake by various age groups within the general population of Canada

Table C-1. Estimates of human daily intake (µg/kg bw/day) of DEE

Route of exposure	0 to 5 months[a] (breast milk-fed)[b]	0 to 5 months[a] (formula fed)[c]	6 to 11 months[d]	1 year[e]	2 to 3 years[f]	4 to 8 years[g]	9 to 13 years[h]	14 to 18 years[i]	Greater than or equal to 19 years[j]
Ambient air[k]	1.76E+0	1.76E+0	1.78E+0	2.18E+0	1.84E+0	1.45E+0	9.93E-1	7.69E-1	6.12E-1
Indoor air[l]	3.32E+2	3.32E+2	3.36E+2	4.12E+2	3.47E+2	2.73E+2	1.87E+2	1.45E+2	1.16E+2
Drinking water[m]	N/A	8.63E+1	5.52E+1	2.15E+1	1.89E+1	1.52E+1	1.16E+1	1.16E+1	1.36E+1
Total intake	3.34E+2	4.19E+2	3.92E+2	4.35E+2	3.67E+2	2.89E+2	2.00E+2	1.57E+2	1.29E+2

Abbreviation: N/A, not applicable

[a] Assumed to weigh 6.3 kg (Health Canada 2015), to breathe 3.7 m^3 of air per day (US EPA 2011), and to ingest 21.6 mg of dust per day (Wilson and Meridian 2015 [modified]). It is assumed that no soil ingestion occurs due to typical caregiver practices.

[b] Exclusively for breast milk-fed infants, assumed to consume 0.744 L of breast milk per day (Health Canada 2018), and breast milk is assumed to be the only dietary source.

[c] Exclusively for formula-fed infants, assumed to drink 0.826 L of water per day (Health Canada 2018), where water is used to reconstitute formula. See footnote on drinking water for details.

[d] Assumed to weigh 9.1 kg (Health Canada 2015), to breathe 5.4 m^3 of air per day (US EPA 2011 [modified]), to drink 0 L of water per day (Health Canada 2017), to ingest 7.3 mg of soil per day, and to ingest 27.0 mg of dust per day (Wilson and Meridian 2015 [modified]). For breast milk-fed infants, assumed to consume 0.632 L of breast milk per day (Health Canada 2018). For formula-fed infants, assumed to drink 0.764 L of water per day (Health Canada 2018), where water is used to reconstitute formula. See footnote on drinking water for details.

[e] Assumed to weigh 11.0 kg (Health Canada 2015), to breathe 8.0 m^3 of air per day (US EPA 2011 [modified]), to drink 0.36 L of water per day (Health Canada 2017), to ingest 8.8 mg of soil per day, and to ingest 35.0 mg of dust per day (Wilson and Meridian 2015 [modified]).

[f] Assumed to weigh 15 kg (Health Canada 2015), to breathe 9.2 m^3 of air per day (US EPA 2011 [modified]), to drink 0.43 L of water per day (Health Canada 2017), to ingest 6.2 mg of soil per day, and to ingest 21.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[g] Assumed to weigh 23 kg (Health Canada 2015), to breathe 11.1 m^3 of air per day (US EPA 2011 [modified]), to drink 0.53 L of water per day (Health Canada 2017), to ingest 8.7 mg of soil per day, and to ingest 24.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[h] Assumed to weigh 42 kg (Health Canada 2015), to breathe 13.9 m^3 of air per day (US EPA 2011 [modified]), to drink 0.74 L of water per day (Health Canada 2017), to ingest 6.9 mg of soil per day, and to ingest 23.8 mg of dust per day (Wilson and Meridian 2015 [modified]).

[i] Assumed to weigh 62 kg (Health Canada 2015), to breathe 15.9 m^3 of air per day (US EPA 2011 [modified]), to drink 1.09 L of water per day (Health Canada 2017), to ingest 1.4 mg of soil per day, and to ingest 2.1 mg of dust per day (Wilson and Meridian 2015 [modified]).

[j] Assumed to weigh 74 kg (Health Canada 2015), to breathe 15.1 m^3 of air per day (US EPA 2011 [modified]), to drink 1.53 L of water per day (Health Canada 2017), to ingest 1.6 mg of soil per day, and to ingest 2.6 mg of dust per day (Wilson and Meridian 2015 [modified]).

[k] The maximum ambient air concentration from Canadian homes (24 µg/m^3) was used for deriving upper-bounding estimates of daily intake for ambient air exposure as a conservative estimate (Chan et al. 1990). Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

[l] The maximum indoor air concentration from Canadian homes (647 µg/m^3) was used for deriving upper-bounding estimates of daily intake for indoor air exposure as a conservative estimate (Chan et al. 1990). Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998).

[m] The maximum concentration measured in a monitoring well network and outwash aquifer (658 µg/L) at the Gloucester Landfill in Canada was used for deriving upper-bounding estimates of daily intake for drinking water exposure as a conservative estimate (Lesage et al. 1990).

Table C-2. Estimates of human daily intake (µg/kg bw/day) of DPE

Route of exposure	0 to 5 months[a] (breast milk-fed)[b]	0 to 5 months[a] (formula fed)[c]	6 to 11 months[d]	1 year[e]	2 to 3 years[f]	4 to 8 years[g]	9 to 13 years[h]	14 to 18 years[i]	Greater than or equal to 19 years[j]
Air[k]	3.69E-3	3.69E-3	3.73E-3	4.57E-3	3.85E-3	3.03E-3	2.08E-3	1.61E-3	1.28E-3
Drinking water[l]	N/A	7.24E-3	4.63E-3	1.81E-3	1.58E-3	1.27E-3	9.73E-4	9.70E-4	1.14E-3
Food and beverages[m]	N/A	N/A	N/A	1.0E-1	1.0E-1	1.0E-1	1.0E-1	1.0E-1	1.0E-1
Total intake	3.69E-3	1.09E-02	8.36E-03	1.06E-01	1.05E-01	1.04E-01	1.03E-01	1.03E-01	1.02E-01

Abbreviation: N/A, not applicable

[a] Assumed to weigh 6.3 kg (Health Canada 2015), to breathe 3.7 m^3 of air per day (US EPA 2011), and to ingest 21.6 mg of dust per day (Wilson and Meridian 2015 [modified]). It is assumed that no soil ingestion occurs due to typical caregiver practices.

[b] Exclusively for breast milk-fed infants, assumed to consume 0.744 L of breast milk per day (Health Canada 2018), and breast milk is assumed to be the only dietary source.

[c] Exclusively for formula-fed infants, assumed to drink 0.826 L of water per day (Health Canada 2018), where water is used to reconstitute formula. See footnote on drinking water for details.

[d] Assumed to weigh 9.1 kg (Health Canada 2015), to breathe 5.4 m^3 of air per day (US EPA 2011 [modified]), to drink 0 L of water per day (Health Canada 2017), to ingest 7.3 mg of soil per day, and to ingest 27.0 mg of dust per day (Wilson and Meridian 2015 [modified]). For breast milk-fed infants, assumed to consume 0.632 L of breast milk per day (Health Canada 2018). For formula-fed infants, assumed to drink 0.764 L of water per day (Health Canada 2018), where water is used to reconstitute formula. See footnote on drinking water for details.

[e] Assumed to weigh 11.0 kg (Health Canada 2015), to breathe 8.0 m^3 of air per day (US EPA 2011 [modified]), to drink 0.36 L of water per day (Health Canada 2017), to ingest 8.8 mg of soil per day, and to ingest 35.0 mg of dust per day (Wilson and Meridian 2015 [modified]).

[f] Assumed to weigh 15 kg (Health Canada 2015), to breathe 9.2 m^3 of air per day (US EPA 2011 [modified]), to drink 0.43 L of water per day (Health Canada 2017), to ingest 6.2 mg of soil per day, and to ingest 21.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[g] Assumed to weigh 23 kg (Health Canada 2015), to breathe 11.1 m^3 of air per day (US EPA 2011 [modified]), to drink 0.53 L of water per day (Health Canada 2017), to ingest 8.7 mg of soil per day, and to ingest 24.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[h] Assumed to weigh 42 kg (Health Canada 2015), to breathe 13.9 m^3 of air per day (US EPA 2011 [modified]), to drink 0.74 L of water per day (Health Canada 2017), to ingest 6.9 mg of soil per day, and to ingest 23.8 mg of dust per day (Wilson and Meridian 2015 [modified]).

[i] Assumed to weigh 62 kg (Health Canada 2015), to breathe 15.9 m^3 of air per day (US EPA 2011 [modified]), to drink 1.09 L of water per day (Health Canada 2017), to ingest 1.4 mg of soil per day, and to ingest 2.1 mg of dust per day (Wilson and Meridian 2015 [modified]).

[j] Assumed to weigh 74 kg (Health Canada 2015), to breathe 15.1 m^3 of air per day (US EPA 2011 [modified]), to

drink 1.53 L of water per day (Health Canada 2017), to ingest 1.6 mg of soil per day, and to ingest 2.6 mg of dust per day (Wilson and Meridian 2015 [modified]).

[k] No monitoring data of air in Canada were identified. Based on an estimate of 6.28 ng/L on the basis of a 100% release scenario to air from ChemCAN v6.00 (ChemCAN 2003) where the simulations conservatively assumed that total quantities were released into a single region of Canada, that is, the Ontario Mixed-Wood Plain region.

[l] Rogers et al. (1986) identified DPE as a component in base/neutral fractions of wastewater and sludge at the Iona Island in British Columbia but the concentration of DPE was not determined. Therefore, no monitoring data where DPE was measured in Canada were identified. Based on an estimate of 0.0552 µg/L on the basis of a 100% release scenario to water from ChemCAN v6.00 (ChemCAN 2003) where the simulations conservatively assumed that total quantities were released into a single region of Canada, that is, the Ontario Mixed-Wood Plain region, at a 100% emission factor and assuming 0% removal for wastewater treatment processes (for water releases).

[m] No definitive information is available concerning the potential use of DPE in foods sold in Canada. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) per capita intake estimate of 5 µg per person per day for the United States (based on annual production volumes reported by the food industry in poundage surveys) was used to derive daily intakes of DPE as a food flavouring agent (see section 6.1.2). In the absence of age group-specific intake estimates, exposures based on a 60 kg person (WHO 2004) were applied to all relevant age groups (1 year of age and older). The bodyweight adjusted intake using a 60 kg bodyweight is considered to be sufficiently conservative to represent the entire population 1 year of age and older (personal communication, emails from FD, Health Canada, to ESRAB, Health Canada, 2019; unreferenced).

Table C-3. Estimates of human daily intake (µg/kg bw/day) of DME

Route of exposure	0 to 5 months[a] (breast milk-fed)[b]	0 to 5 months[a] (formula fed)[c]	6 to 11 months[d]	1 year[e]	2 to 3 years[f]	4 to 8 years[g]	9 to 13 years[h]	14 to 18 years[i]	Greater than or equal to 19 years[j]
Air[k]	7.21E+1	7.21E+1	7.28E+1	8.93E+1	7.53E+1	5.92E+1	4.06E+1	3.15E+1	2.50E+1
Drinking water[l]	N/A	7.60E-3	4.87E-3	1.90E-3	1.66E-3	1.34E-3	1.02E-3	1.02E-3	1.20E-3
Total intake	7.21E+1	7.21E+1	7.28E+1	8.93E+1	7.53E+1	5.92E+1	4.06E+1	3.15E+1	2.50E+1

Abbreviation: N/A, not applicable.

[a] Assumed to weigh 6.3 kg (Health Canada 2015), to breathe 3.7 m^3 of air per day (US EPA 2011), and to ingest 21.6 mg of dust per day (Wilson and Meridian 2015 [modified]). It is assumed that no soil ingestion occurs due to typical caregiver practices.

[b] Exclusively for breast milk-fed infants, assumed to consume 0.744 L of breast milk per day (Health Canada 2018), and breast milk is assumed to be the only dietary source.

[c] Exclusively for formula-fed infants, assumed to drink 0.826 L of water per day (Health Canada 2018), where water is used to reconstitute formula. See footnote on drinking water for details.

[d] Assumed to weigh 9.1 kg (Health Canada 2015), to breathe 5.4 m^3 of air per day (US EPA 2011 [modified]), to drink 0 L of water per day (Health Canada 2017), to ingest 7.3 mg of soil per day, and to ingest 27.0 mg of dust per day (Wilson and Meridian 2015 [modified]). For breast milk-fed infants, assumed to consume 0.632 L of breast milk per day (Health Canada 2018). For formula-fed infants, assumed to drink 0.764 L of water per day (Health Canada 2018), where water is used to reconstitute formula. See footnote on drinking water for details.

[e] Assumed to weigh 11.0 kg (Health Canada 2015), to breathe 8.0 m^3 of air per day (US EPA 2011 [modified]), to drink 0.36 L of water per day (Health Canada 2017), to ingest 8.8 mg of soil per day, and to ingest 35.0 mg of dust per day (Wilson and Meridian 2015 [modified]).

[f] Assumed to weigh 15 kg (Health Canada 2015), to breathe 9.2 m^3 of air per day (US EPA 2011 [modified]), to drink 0.43 L of water per day (Health Canada 2017), to ingest 6.2 mg of soil per day, and to ingest 21.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[g] Assumed to weigh 23 kg (Health Canada 2015), to breathe 11.1 m^3 of air per day (US EPA 2011 [modified]), to

drink 0.53 L of water per day (Health Canada 2017), to ingest 8.7 mg of soil per day, and to ingest 24.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[h] Assumed to weigh 42 kg (Health Canada 2015), to breathe 13.9 m^3 of air per day (US EPA 2011 [modified]), to drink 0.74 L of water per day (Health Canada 2017), to ingest 6.9 mg of soil per day, and to ingest 23.8 mg of dust per day (Wilson and Meridian 2015 [modified]).

[i] Assumed to weigh 62 kg (Health Canada 2015), to breathe 15.9 m^3 of air per day (US EPA 2011 [modified]), to drink 1.09 L of water per day (Health Canada 2017), to ingest 1.4 mg of soil per day, and to ingest 2.1 mg of dust per day (Wilson and Meridian 2015 [modified]).

[j] Assumed to weigh 74 kg (Health Canada 2015), to breathe 15.1 m^3 of air per day (US EPA 2011 [modified]), to drink 1.53 L of water per day (Health Canada 2017), to ingest 1.6 mg of soil per day, and to ingest 2.6 mg of dust per day (Wilson and Meridian 2015 [modified]).

[k] Based on the NPRI air emission data and facility-specific information, the US EPA model SCREEN3 was selected to estimate concentration in ambient air (123 µg/m^3).

[l] No monitoring data of water Canada were identified. Based on an estimate of 0.058 µg/L on the basis of a 100% release scenario to water from ChemCAN v6.00 (ChemCAN 2003) where the simulations conservatively assumed that total quantities were released into a single region of Canada, that is, the Ontario Mixed-Wood Plain region, at a 100% emission factor and assuming 0% removal for wastewater treatment processes (for water releases).