

# **Draft Screening Assessment**

## ***Ethylene Glycol Ethers***

### **Chemical Abstracts Service Registry Numbers**

**110-71-4**

**111-46-6**

**111-90-0**

**112-07-2**

**112-27-6**

**112-34-5**

**112-60-7**

**Environment and Climate Change Canada  
Health Canada**

**March 2017**

## Synopsis

Pursuant to sections 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of Environment and the Minister of Health have conducted a screening assessment of seven substances referred to herein as the Ethylene Glycol Ethers Group. The substances in this group were identified as priorities for assessment as they met the categorization criteria under subsection 73(1) of CEPA. The Chemical Abstracts Service Registry Numbers (CAS RN<sup>1</sup>), their *Domestic Substances List* (DSL) names and their common names and acronyms are listed in the table below.

### Substances in the Ethylene Glycol Ethers Group

CAS RN	DSL name	Common name	Acronyms
111-46-6	Ethanol, 2,2'-oxybis-	Diethylene glycol	DEG
112-27-6	Ethanol, 2,2'-[1,2-ethanediylbis(oxy)]bis-	Triethylene glycol	TEG
112-60-7	Ethanol, 2,2'-[oxybis(2,1-ethanediylloxy)]bis-	Tetraethylene glycol	TTEG
111-90-0	Ethanol, 2-(2-ethoxyethoxy)-	Diethylene glycol monoethyl ether	DEGEE
112-07-2	Ethanol, 2-butoxy-, acetate	Ethylene glycol monobutyl ether acetate	EGBEA
112-34-5	Ethanol, 2-(2-butoxyethoxy)-	Diethylene glycol monobutyl ether	DEGBE
110-71-4 <sup>a</sup>	Ethane, 1,2-Dimethoxy-	Monoglyme or Ethylene glycol dimethyl ether	EGDME

<sup>a</sup> This substance was not identified under subsection 73(1) of CEPA but was included in this assessment as it was considered a priority based on other human health concerns.

Two other substances (CAS RN 111-96-6 and 112-49-2) were identified as being part of the Ethylene Glycol Ethers Group on the two-year rolling risk assessment publication plan published in May 2016. These two substances were considered in the *Ecological Risk Classification of Organic Substances and Human Health Threshold of Toxicological Concern* science approach and were identified as being of low concern to both health and the environment. As such, they are not further addressed in this report. Regulatory conclusions for these two substances will be provided in a future assessment publication that addresses a range of substances in this situation.

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In Canada, substances in the Ethylene Glycol Ethers Group are used in a variety of applications, including cosmetics and non-prescription drugs, paints and coating products, air fresheners, household cleaning products, as well as in adhesives, batteries, and textiles.

All of the substances in this group are imported into Canada at quantities ranging from 100 to 10 000 000 kg/year. Four of the seven substances (TTEG, DEGEE, EGBEA and DEGBE) are manufactured in Canada at quantities ranging from 1000 to 10 000 000 kg/year. In the United States, production volumes range from 10 000 000 to 450 000 000 kg/year for these substances.

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

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

For the human health risk assessment, the seven substances in this group were separated into three subgroups: ethylene glycols (EGs), ethylene glycol ethers (EGEs), and glymes. Environmental media and food were not identified as significant sources of exposure to Canadians. For the EGs and EGEs, estimates of exposure were derived based on levels of substances in products used by consumers, such as cosmetics and non-prescription drugs, paint and coating products, air fresheners, and household cleaning products. For monoglyme, estimates of exposure were based on levels in indoor air and from use of air fresheners.

Systemic toxicity is observed at high dose levels in laboratory animals exposed to ethylene glycol ethers, with target organs being the liver and kidney. For monoglyme, developmental toxicity is observed in laboratory animals at doses lower than those for the other Ethylene Glycol Ethers in this group. Effects on testes, blood, thymus and adrenal glands are also observed.

For all subgroups, based on the estimates of exposure for products used by consumers and on critical effect levels identified from laboratory studies, margins of exposure are considered to be adequate to address uncertainties in the health effects and exposure databases.

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

Therefore, it is proposed to conclude that the seven substances in the Ethylene Glycol Ethers group in this draft screening assessment do not meet any of the criteria under section 64 of CEPA.

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## 1. Introduction

Pursuant to sections 68 and 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health conduct screening assessments of substances to determine whether they present or may present a risk to the environment or to human health. The seven substances addressed in this draft screening assessment are referred to collectively as the Ethylene Glycol Ethers. They were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA (Environment and Climate Change Canada, Health Canada [modified 2007]), or were considered a priority based on other human health concerns.

Two other substances (CAS RNs 111-96-6 and 112-49-2) were identified as being part of the Ethylene Glycol Ethers Group on the two-year rolling risk assessment publication plan published in May 2016 (ECCC 2016c). These two substances were considered in the Ecological Risk Classification of Organic Substances and Human Health Threshold of Toxicological Concern science approach documents (Health Canada 2016c) and were identified as being of low concern to both health and the environment. As such, they are not further addressed in this report. Regulatory conclusions for these two substances will be provided in a future assessment publication that addresses a range of substances in this situation.

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

Substances in the Ethylene Glycol Ethers Group were reviewed internationally through different programs, such as the Organisation for Economic Cooperation and Development's Cooperative Chemicals Assessment Programme, and by the European Commission (a number of assessments are available). These assessments undergo rigorous review and endorsement by international governmental authorities. Environment and Climate Change Canada and Health Canada are active participants in this process and consider these assessments to be reliable. The data in these assessments will be used to inform the health effects characterization for the Ethylene Glycol Ethers Group.



This draft screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposure, including additional information submitted by stakeholders. Relevant data were identified up to April 2016. However, more recent studies or information provided via internal and external peer consultation may also be cited. Empirical data from key studies as well as results from models were used to reach proposed conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

This draft screening assessment was prepared by staff in the CEPA Risk Assessment Programs at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. Comments on the ERC approach and results were received from Dr. Jon Arnot (ARC Arnot Research and Consulting) and Mr. Geoff Granville (GCGranville Consulting Corp.). Additionally, the ERC document was subject to a 60-day public comment period. The human health portions of this screening assessment have undergone external peer review and/or consultation. Comments on the technical portions relevant to human health were received from Lisa Sweeney (Henry M. Jackson Foundation for the Advancement of Military Medicine), Chris Bevan (CJB Consulting LLC.), Ray York (RG York and Associates LLC), and John Reichard (Toxicology Excellence for Risk Assessment Center, University of Cincinnati). While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Environment and Climate Change Canada and Health Canada.

This draft screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA, by examining scientific information and incorporating a weight-of-evidence approach and precaution.<sup>3</sup> The draft screening assessment presents the critical information and considerations on which the proposed conclusion is based.

## 2. Identity of Substances

The seven substances assessed in this screening assessment belong to a larger chemical group of substances known as glycol ethers. The general formula for glycol

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<sup>3</sup>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 used by 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 hazardous products intended for workplace use, handling and storage. 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.

ethers is shown in Figure 2-1. Glycol ethers may be subgrouped based on the nature of the functional groups (R1 or R2), the number of glycol units, the number of carbon atoms in the ether side chain (R1 or R2) or the degree of branching in R3 and R4 (Mangelsdorf et al. 2016). Glycol esters with acetic acid, also known as glycol ether acetates, are also included in the chemical group (Mangelsdorf et al. 2016).

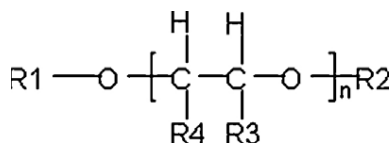
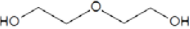

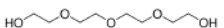

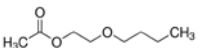


Figure 2-1. General structural formula of glycol ethers, glycol esters and glycol diethers (from Mangelsdorf et al. 2016).

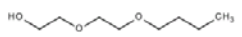
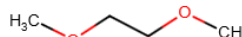
The Chemical Abstracts Service Registry Numbers (CAS RN<sup>4</sup>), Domestic Substances List (DSL) names, common names, and acronyms for the individual substances in the Ethylene Glycol Ethers are presented in Table 2-1. A list of additional chemical names (e.g., trade names) is available from the National Chemical Inventories (NCI 2015).

The seven substances discussed in this screening assessment are representative substances from three different subgroups: ethylene glycols (EGs), ethylene glycol ethers (EGEs) and glymes (see Tables 2-1 and 2-2).

**Table 2-1. Substance identities for Ethylene Glycol Ethers**

CAS RN (acronym)	DSL name (common name) <sup>a</sup>	Chemical structure and molecular formula	Molecular weight (g/mol)
111-46-6 (DEG)	Diethylene Glycol		106.12
112-27-6 (TEG)	Triethylene Glycol		150.17
112-60-7 (TTEG)	Tetraethylene Glycol		194.23
111-90-0 (DEGEE)	Diethylene Glycol Monoethyl Ether		134.17
112-07-2 (EGBEA)	2-Butoxyethyl Acetate		160.21

<sup>4</sup> The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior, written permission of the American Chemical Society.

CAS RN (acronym)	DSL name (common name) <sup>a</sup>	Chemical structure and molecular formula	Molecular weight (g/mol)
112-34-5 (DEGBE)	2-(2-Butoxyethoxy) ethanol		162.23
110-71-4 (EGDME)	Monoglyme		90.12

a. ChemIDplus 1993a,b,c,d,e, f,g

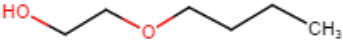
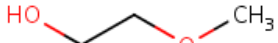
**Table 2-2. Subgroups of Ethylene Glycol Ethers substances**

Subgroup	Chemicals	Critical functional groups	Molecular weight range (g/mol)
Ethylene Glycols (n=3)	DEG, TEG, TTEG	Ethylene glycol ethers that consist of 1, 2, or 3 glycol ether groups with 2 terminal alcohol groups	106.12–194.23
Ethylene Glycol Ethers (n=3)	DEGEE, EGBEA, DEGBE	Ethylene glycol ethers that consist of 1 or 2 glycol ether groups with 1 terminal alkyl group of 2 or 4 carbons and 1 terminal alcohol or ester group	134.17–162.23
Glymes (n=1)	Monoglyme	Ethylene glycol ether consisting of two glycol ether units and two terminal methyl groups.	90.12

## 2.1 Selection of Analogues

A read-across approach using data from analogues has been used to inform the human health assessments. The analogues selected were structurally similar and/or functionally similar to substances within this group (e.g., based on physical-chemical properties and toxicokinetics) and had relevant empirical data that could be used to read-across to substances that were data poor. In addition to the analogues, read-across from one substance to another within the EGs subgroup are discussed in the relevant sections of this report (see Health effects assessment of the Ethylene Glycols subgroup). A list of the analogues used to inform this assessment is presented in Table 2-3 along with an indication of the potential read-across data.

**Table 2-3. Analogue identity and availability of read-across data used in this assessment**

CAS RN for analogue	DSL/other name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)	Human health data	Target substance for analogue
111-76-2 <sup>a</sup>	2-Butoxy-ethanol (EGBE: Ethylene glycol monobutyl ether)	 $C_6H_{14}O_2$	118.18	Y	EGBEA (CAS RN 112-07-2) <sup>a</sup>
109-86-4 <sup>b</sup>	2-Methoxy-ethanol (2-ME)	 $C_3H_8O_2$	76.09	Y <sup>c</sup>	Monoglyme (CAS RN 110-71-4) <sup>b</sup>

<sup>a</sup> EGBE chemical structure, molecular formula and molecular weight from ChemIDplus 1993h.

<sup>b</sup> 2-ME chemical structure, molecular formula and molecular weight from ChemIDplus 1993i.

<sup>c</sup> As shown in the “Health effects assessment of Monoglyme” section, 2-ME is actually a metabolite of monoglyme in experimental animals.

### 3. Physical and Chemical Properties

Generally, glycol ethers are high boiling point, semi-volatile liquids that behave as solvents for water and many organic liquids (Mangelsdorf et al. 2016). The EG, EGE, and monoglyme subgroups have different melting and boiling point, specific gravity, density, and vapour pressure ranges. Furthermore, monoglyme shows a higher vapour pressure, higher log octanol-water partition coefficient (Kow) and lower boiling point than substances in the other two subgroups and this may be due in part to its low molecular weight.

A summary of physical and chemical properties of the substances in the Ethylene Glycol Ethers group are presented in Tables 3-1, 3-2 and 3-3. Physical-chemical properties of the individual substances in the EG and EGE subgroups may be found in the supporting document (Health Canada 2016a). Additional physical and chemical properties are presented in ECCC (2016b).

**Table 3-1. Range of chemical and physical properties for ethylene glycols**

Property	Type	Value	Temperature (°C)	Reference
Physical form	-	Liquid	25	-
Melting point (°C)	Experimental	-10 to -6.2	NA	Lide 2007 HSDB 2007b
Boiling point (°C)	Experimental	246–327.3	NA	Lide 2007 HSDB 2007b
Specific gravity (dimensionless)	Experimental	1.1197–1.1285	25; 15	Lide 2007 HSDB 2007b
Density (kg/m <sup>3</sup> )	Experimental	1119.7–1128.5	25; 15	Lide 2007 HSDB 2007b
Vapour pressure (mmHg)	Experimental	$4.65 \times 10^{-5}$ – $5.7 \times 10^{-3}$	26; 25	HSDB 1983c HSDB 2007a,b
Henry's Law constant (atm·m <sup>3</sup> /mol)	Estimated; Experimental	$2.61 \times 10^{-10}$ – $2.0 \times 10^{-9}$	25; NS	HSDB 2007a HSDB 2009a
Log K <sub>ow</sub> (dimensionless)	Modelled; Estimated	-2.02 to -1.47	NS	HSDB 2007b HSDB 2009a
Water solubility (mg/L)	Experimental	$1 \times 10^6$	20	HSDB 2007a,b HSDB 2009a

**Table 3-2. Range of chemical and physical properties for ethylene glycol ethers**

Property	Type	Value	Temperature (°C)	Reference
Physical form	-	Liquid	25	-
Melting point (°C)	Experimental	-68.1 to -54	NA	HSDB 2007c,d
Boiling point (°C)	Experimental	192–230.4	NA	HSDB 2007b HSDB 2009b
Specific gravity (dimensionless)	Experimental	0.9422–0.9885	20	HSDB 2007c HSDB 2009b
Density (kg/m <sup>3</sup> )	Experimental	942.2–988.5	20	HSDB 2007c HSDB 2009b
Vapour pressure (mmHg)	Experimental	0.0219–0.375	25; 20	HSDB 2007d HSDB 2009b
Henry's Law constant (atm·m <sup>3</sup> /mol)	Experimental	$7.29 \times 10^{-9}$ – $5.46 \times 10^{-6}$	25	HSDB 2007d HSDB 2009b
Log K <sub>ow</sub> (dimensionless)	Experimental; Estimated	-0.54 to 1.57	NS	HSDB 2007c HSDB 2009b
Water solubility (mg/L)	Experimental	$9 \times 10^3$ – $1 \times 10^6$	20	HSDB 2007c,d HSDB 2009b

**Table 3-3. Physical and chemical property values for monoglyme**

Property	Type	Value	Temperature (°C)	Reference
Physical Form	-	Liquid	25	-
Melting point (°C)	Experimental	-71 to -58	NA	HSDS 2002
Boiling point	Experimental	82–83	NA	HSDS 2002

Property	Type	Value	Temperature (°C)	Reference
(°C)				
Specific gravity (dimensionless)	Experimental	0.86285	20; 4	HSDS 2002
Density (kg/m <sup>3</sup> )	Experimental	862.85	25; 15	HSDS 2002
Vapour pressure (mmHg)	Experimental	48	20	HSDS 2002
Henry's Law constant (atm-m <sup>3</sup> /mol)	Estimated	$1.1 \times 10^{-6}$	25	HSDS 2002
Log K <sub>ow</sub> (dimensionless)	Modelled; Estimated	-0.21	NA	HSDS 2002
Water solubility (mg/L)	Experimental	$1 \times 10^6$	20	HSDS 2002

NA = Not available.

## 4. Sources

All seven substances in this group are commercially produced and do not occur naturally.

Three separate surveys, issued pursuant to section 71 of CEPA, were conducted in 2001, 2008 and 2012 to obtain information about quantities in commerce for various substances in Canada (Environment Canada 2001, 2009, 2014).

The section 71 surveys indicated that one substance in the EGs subgroup, TTEG, and all three substances in the EGEs subgroup were manufactured in Canada above the reporting threshold. All seven substances in the Ethylene Glycol Ethers group were imported into Canada above the reporting threshold (Environment Canada 2001, 2009, 2014; see Table 4-1).

**Table 4-1. Summary of Canadian manufacture and import of substances in the Ethylene Glycol Ethers group<sup>a</sup>**

Subgroup	Common name	Total manufacture (kg)*	Total imports (kg)*
Ethylene Glycols	DEG	-	100 000–1 000 000
	TEG	-	1 000 000–10 000 000
	TTEG	1 000 000–10 000 000	100 000–1 000 000
Ethylene Glycol Ethers	DEGEE	10 000–100 000	100 000–1 000 000
	EGBEA	1000–10 000	100 000–1 000 000
	DEGBE	10 000–100 000	1 000 000–10 000 000
Glymes	Monoglyme	-	100–100 000

<sup>a</sup> Values reflect quantities reported in response to a survey conducted under section 71 of CEPA (Environment Canada 2001, 2009, 2014). See survey for specific inclusions and exclusions (schedules 2 and 3).

In the United States (US), production volumes ranged from 10 000 000 to 450 000 000 kg for the EG and EGE substances in 2012 (US EPA 2012) and from 453 600 to 4 536 000 for monoglyme in 2005 (ECHA 2012b).<sup>5</sup> In the European Union, manufacture and import of all seven substances ranged from 100 000 to 1 000 000 000 kg in 2015 (ECHA 2015).

## 5. Uses

The two section 71 survey results included information about the uses in Canada of all six substances in the EGs and EGEs subgroups; they are presented in Table 5-1 (Environment Canada 2001, 2014).

<sup>5</sup> US production volumes for the year 2005, submitted to the European Chemicals Agency (ECHA 2012b). The US Chemical Data Reporting database did not cite 2012 production volumes for monoglyme as it was listed as confidential business information (US EPA 2012).



**Table 5-1. Summary of Canadian non-confidential business information uses of substances in the EGs and EGEs subgroups**

<b>Major uses<sup>a</sup></b>	<b>Ethylene Glycols</b>	<b>Ethylene Glycol Ethers</b>
Adhesives	TEG, TTEG	EGBEA, DEGBE
Automotive, aircraft and transportation	DEG, TEG, TTEG	DEGEE, EGBEA, DEGBE
Cleaning products <sup>b</sup>	DEG, TEG	DEGEE, EGBEA, DEGBE
Personal care products <sup>c</sup> , including cosmetics	-	DEGEE
Dyes and pigments	-	DEGEE, DEGBE
Medical, health products and veterinary	-	DEGEE
Paints and coatings <sup>b</sup>	DEG, TEG, TTEG	DEGEE, EGBEA, DEGBE
Plastics and plasticizers	TEG, TTEG	DEGEE, DEGBE
Printing and writing products and printing inks	TEG, TTEG	DEGEE, DEGBE
Rubber	TEG	DEGBE
Textile, leather and tanning	-	DEGEE
Toys, sporting equipment and playground equipment	-	EGBEA

<sup>a</sup>. All information obtained from section 71 surveys under CEPA 1999 (Environment Canada 2001, 2014).

<sup>b</sup> Submitted section 71 data along with MSDS concentration data were used to characterize exposure in Section 7.

<sup>c</sup> For the purpose of this document, a personal care product is a product that is generally recognized by the public for use in daily cleansing or grooming. Depending on how the product is represented for sale and its composition, personal care products may fall into one of three regulatory categories in Canada: cosmetics, drugs or natural health products.

DEG is not permitted in oral or leave-on cosmetic products<sup>6</sup> (Health Canada [modified 2015]). Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, TEG, DEGEE and DEGBE were notified to be present in cosmetic products<sup>7</sup> (personal communication, emails from the Consumer Product Safety Directorate (CPSD), Health Canada, to the Existing Substances Risk Assessment Bureau (ESRAB), Health Canada, dated September 2015; unreferenced).

TEG and DEGBE are listed in the Drug Product Database as being present as active ingredients in hard-surface disinfectant drugs (DPD 2016). DEG, TEG, DEGEE and DEGBE are listed in the Therapeutic Product Directorate's internal Non-Medical Ingredients Database as being present in human and disinfectant drugs.<sup>8</sup> DEG and DEGBE are listed in the Natural Health Products Ingredients Database (NHPID) with a non-medicinal role for topical use only, as a fragrance ingredient, solvent, or viscosity decreasing agent, but not found to be present in currently licensed natural health products (LNHPD 2016; NHPID 2016). TEG and DEGEE are also listed in the NHPID with a non-medicinal role for topical use only, as a fragrance ingredient, solvent, or viscosity decreasing agent, and are listed as being present in currently licensed natural health products in the Licensed Natural Health Products Database<sup>9</sup> (LNHPD 2016; NHPID 2016). Product types in natural health products and human and disinfectant drugs are medicinal shampoos, hand sanitizing liquids, sunscreen, facial cleansers, acne treatments, etc.

In Canada, the six substances in the EGs and EGEs subgroups are used in food packaging; however, only DEG and EGBEA could be in direct contact with food (personal communication, emails from the Food Directorate, Health Canada, to the Risk

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<sup>6</sup> The List of Prohibited and Restricted Cosmetic Ingredients (more commonly referred to as the Cosmetic Ingredient Hotlist or simply the Hotlist) is an administrative tool that Health Canada uses to communicate to manufacturers and others that certain substances, when present in a cosmetic, may contravene the general prohibition found in section 16 of the *Food and Drugs Act* or a provision of the *Cosmetic Regulations* (Health Canada 2011a).

<sup>7</sup> Cosmetic product types: Face and body moisturizer, tanning products, hair dye, make-up and nail polish remover, genitalia cream, hair shampoo and conditioner, hair styling products, and face and body cleanser.

<sup>8</sup> Human and disinfectant drugs are products that have been issued drug identification numbers (DINs) based on the non-medicinal ingredients they contain. They include, but are not limited to: medicinal shampoo; antibacterial soaps; disinfectant sprays, solutions or cleaners; and gels, creams or solutions for treating muscle pains, joint pains and skin conditions.

<sup>9</sup> Natural health product types include, but are not limited to, acne therapy, counterirritant, medicated skin care, and sunscreen products.

Management Bureau, Health Canada, dated October 2015; unreferenced). None of the substances are listed in the List of Permitted Food Additives as approved food additives under the *Food and Drugs Act* and associated Marketing Authorizations (personal communication, emails from the Food Directorate, Health Canada, to the Risk Management Bureau, Health Canada, dated October 2015; unreferenced).

Finally, five of the six substances in the EGs and EGEs subgroups (DEG, TEG, DEGEE, EGBEA and DEGBE) are identified as formulants in pest control products. Only TEG is a registered active pesticidal ingredient, but the registered product is only formulated in Canada and exported (personal communication, emails from the Pest Management Regulatory Agency, Health Canada to the ESRAB, Health Canada, dated September 2015 and September 2016; unreferenced).

Monoglyme is used as an additive at concentrations ranging from 1 to 10% w/w in lithium for the manufacture of all types of batteries based on material safety data sheets (MSDSs) for products in Canada. Monoglyme is also found as an impurity in air fresheners and laundry products at concentrations less than 0.01% (Environment Canada 2009). Monoglyme is identified in the Therapeutic Products Directorate's guidance document *Q3C(R5): Impurities: Guideline for Residual Solvents* as a Class 2 solvent and should therefore not exceed 100 ppm (equal to 1.0 mg/day permissible daily exposure) in drugs (Health Canada 2016b).

Major uses identified internationally for the EGs and EGEs subgroup substances, in addition to those listed in Table 5-1, include antifreeze, do-it-yourself materials, pest control products, indirect additives in food contact substances, and industrial or commercial use (JECFA 1995; Wagner 2006; Tønning et al. 2008; OECD 2007, 2009a; Scorecard 2011; US FDA 2011; GoodGuide 2014; CCOHS 2015; DOW 2015; ECHA 2015; EWG 2015; NICNAS 2015; NYSDEC 2015; U.S. Government Publishing Office 2015). Major uses identified internationally for monoglyme include cleaning products, medical, health and veterinary products, paints and coatings, printing, writing products and printing inks, and industrial or commercial use (ECHA 2012b; NICNAS 2016a).

Identified uses in Canada, carried forward for exposure assessment are outlined in Section 7.1.2. Briefly, exposures to the substances in this group were characterized for waterborne paints, wood sealant/stains, personal care products,<sup>10</sup> air fresheners, household cleaning products, and painted toys. There are also potential infrequent exposures from other products, such as adhesives, batteries and textiles (Environment Canada 2001, 2009, 2014; see Table 5-1).

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<sup>10</sup> For the purpose of this document, a personal care product is a product that is generally recognized by the public for use in daily cleansing or grooming. Depending on how the product is represented for sale and its composition, personal care products may fall into one of three regulatory categories in Canada: cosmetics, drugs or natural health products.

## 6. Potential to Cause Ecological Harm

### 6.1 Characterization of Ecological Risk

The ecological risk of the seven substances in the Ethylene Glycol Ethers group was 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 based on weighted consideration of multiple lines of evidence for determining risk classification. The various lines of evidence are combined to discriminate between substances of lower or higher potency and lower or higher potential for exposure in various media. This approach reduces the overall uncertainty with risk characterization compared to an approach that relies on a single metric in a single medium (e.g.,  $LC_{50}$ ) for characterization. This section 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, fish bioconcentration), acute fish ecotoxicity, and chemical import or manufacture volume in Canada were either collected from scientific literature, from available empirical databases (e.g., OECD QSAR Toolbox) and from responses to surveys under section 71 of CEPA or were generated using selected quantitative structure-activity relationship (QSAR) 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 based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity were established. Exposure profiles were also composed of multiple metrics, including potential emission rate, overall persistence, and long-range transport potential. Hazard and exposure profiles were compared to decision criteria in order to classify the hazard and exposure potentials for each organic substance as low, moderate or high. Additional rules were applied (e.g., classification consistency, margin of exposure) to refine the preliminary classifications of hazard or exposure.

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

ERC uses a weighted approach to minimize the potential for both over- and under-classification of hazard and exposure and subsequent risk. The balanced approaches for dealing with uncertainties are described in greater detail in ECCC (2016a). The following describes two of the more substantial areas of uncertainty. Error with empirical or modeled acute toxicity values could result in changes in classification of hazard, particularly metrics relying on tissue residue values (i.e., mode of toxic action), many of which are predicted values from QSAR models. However, the impact of this error is mitigated by the fact that overestimation of median lethality will result in a conservative (protective) tissue residue 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 classifications thus reflect exposure and risk in Canada based on what is believed to be the current use quantity and may not reflect future trends.

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

The hazard and exposure classifications of the seven substances in the Ethylene Glycol Ethers group are summarized in Table 6-1.

**Table 6-1. Ecological risk classification results for substances in the Ethylene Glycol Ethers group**

<b>Substance (CAS RN)</b>	<b>ERC hazard classification</b>	<b>ERC exposure classification</b>	<b>ERC risk classification</b>
DEG (111-46-6)	low	low	low
TEG (112-27-6)	low	low	low
TTEG (112-60-7)	low	low	low
DEGEE (111-90-0)	low	low	low
EGBEA (112-07-2)	low	low	low
DEGBE (112-34-5)	low	low	low
[EGDME] (110-71-4)	low	low	low

Based on low hazard and low exposure classifications according to ERC for the seven substances in the Ethylene Glycol Ethers group, these substances were classified as having a low potential for ecological risk. It is therefore unlikely that these substances result in concerns for organisms or the broader integrity of the environment in Canada.

## 7. Potential to Cause Harm to Human Health

### 7.1 Exposure Assessment

#### 7.1.1 Environment media and food

Measured concentrations of the seven substances in this group in ambient air, water, and food were not identified in Canada.<sup>11</sup>

Two substances, DEGBE and EGBEA, were reported as released to air in Canada at a rate of 20 389 and 10 876 tons/year, respectively, in 2013 (NPRI 1993–2013). Based on this information and using commercial quantities reported in Canada of all six substances in the EGs and EGEs subgroups and monoglyme, concentrations were modelled (using ChemCAN version 6.0) in environmental matrices after emission into air. Using these modelled estimates for each substance, drinking water intakes were derived, which resulted in nanogram-level or minimal exposures (<1 to 45 ng/kg bw/day, depending on the substance) (Health Canada 2016a).

In Canada, all seven substances in this group are used in food packaging. However, only DEG and EGBEA could potentially be in contact with food (personal communication, emails from the HPFB, Health Canada, to the RMB, Health Canada, dated October 2015; unreferenced). Probable exposure was estimated to be 0.3 and 0.03 ug/kg bw/day for DEG and EGBEA, respectively.

DEGEE was surveyed in a comprehensive indoor air study conducted in 18 cities and towns across Canada (2009 to 2011). It was detected in 3% of the 3857 residences at a geometric mean of 0.54 µg/m<sup>3</sup> with a range of 0.4 to 6.93 µg/m<sup>3</sup> (Zhu et al. 2013 a, b). Monoglyme was reported in indoor air in Germany at a maximum concentration of 13 µg/m<sup>3</sup> (95th percentile: 0.5 µg/m<sup>3</sup>) based on 12 of 500 measurements (ECHA 2012b).<sup>12</sup>

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<sup>11</sup> Elsewhere, two of these substances have been measured in water, air and soil. DEG has been reported in soil (ATSDR 2013). DEGEE has been reported in air (NYSDEC 2011) and water (OECD 2007).

<sup>12</sup> ECHA (2012b) mentioned two separate surveys in Germany, one showing a maximum of 13 µg/m<sup>3</sup> based on 12/500 measurements and the other showing a maximum of 5 µg/m<sup>3</sup> based on 8/23 measurements. It was not specified whether the measurements represented separate residences or not and the source documents were not available.

DEG has been reported to be present in soil from hazardous waste sites or facilities in the US; however, the value reported was not relevant to this assessment (ASTDR 2013).

## 7.1.2 Products used by consumers

### Derivation of dermal absorption values

DEG dermally applied to rat skin *in vivo* was rapidly absorbed, and 15 minutes after application, approximately 50% of the dose, based on radioactivity, was located in the skin.<sup>13</sup> Eight and 24 hours after dermal application, radioactivity of 12 and 32%, respectively, was detected in rat urine, thus indicating dermal absorption and systemic exposure (DOW 1981). Based on these unpublished dermal data for DEG submitted to Health Canada, dermal absorption for TEG and TTEG was considered to be 50% (DOW 2016a).

For DEGEE, three well-conducted *in vitro* studies on dermal absorption through human skin tested a shampoo formulation containing 5 or 10% DEGEE, a hydro-alcoholic (leave on) formulation containing 15% DEGEE, and emulsified (leave on) formulations containing 2, 5 or 10% DEGEE. Total absorption was 21.6 and 17.5%, 51.5%, and 43.2 to 56%, respectively, for the three studies (SCCP 2006a). Based on these studies, dermal absorption was considered to be 50% for DEGEE.

For DEGBE, none of the available studies on dermal absorption in human or rat skin were suitable for derivation of a dermal absorption value. However, based on these same experiments and well-conducted dermal absorption studies with DEGEE and EGBE, SCCP (2006b) stated that "... it is unlikely that the dermal absorption is larger than 50%."

As shown in Section 7.2.2, once absorbed, EGBEA is rapidly hydrolysed in blood to EGBE and acetate, and all systemic effects observed with EGBEA are typically also observed with EGBE. Based on studies in rats, pigs and humans, a range of absorption values were observed, but in general, dermal absorption of liquid EGBE varied between 20 and 30% in rats, and EC (2006-2008a) stated that, "for the dermal route, extrapolation is likely to be equal or less than EGBE. It can be anticipated that dermal penetration of liquid EGBEA would be of about 30% and vapour EGBEA of about 39%." Thus, based on the available information for EGBE, a dermal absorption value of 30% was selected for EGBEA.

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<sup>13</sup> This was based on 75 uL test substance applied to 6.25 cm<sup>2</sup> dorsal surface but the authors did not state the dose in mg/kg bw. The other study applied 50 mg to 12 cm<sup>2</sup> dorsal surface.



A summary of the dermal absorption values is presented in Table 7-1.

**Table 7-1. Summary of dermal absorption values for substances in the EGEs group**

Substance (CAS RN)	Dermal absorption	Reference
DEG (111-46-6)	50%	DOW 1981, 2016a
TEG (112-27-6)	50% <sup>a</sup>	DOW 2016a
TTEG (112-60-7)	50% <sup>a</sup>	DOW 2016a
DEGEE (111-90-0)	50%	SCCP 2006a
EGBEA (112-07-2)	30%	EC 2006-2008a
DEGBE(112-34-5)	50%	SCCP 2006b

<sup>a</sup> Using dermal absorption reported for DEG as a surrogate.

### **Cosmetics, natural health products, and over the counter drugs<sup>14</sup>**

Based on notifications to Health Canada, three substances in this group (TEG DEGEE, DEGBE) are in cosmetic products in Canada<sup>15</sup> (personal communication, emails from the CPSD, Health Canada, to the ESRAB, Health Canada, dated September 2015; unreferenced). TEG and DEGEE are also present as non-medicinal ingredients in natural health products in Canada (LNHPD 2016).<sup>16</sup> Health Canada internal sources of information indicated that DEG, TEG and DEGEE are also used as non-medicinal ingredients in human and disinfectant drugs (personal communication, emails from the Health Products and Food Branch, Health Canada, to the Risk Management Bureau, Health Canada, dated October 2015; unreferenced).

<sup>14</sup> Cosmetics, natural health products and drugs are three regulatory categories in Canada. For the purposes of this document, they may also be considered collectively as personal care products.

<sup>15</sup> Cosmetic product types include, but are not limited to: face and body moisturizers, tanning products, hair dyes, make-up and nail polish removers, genitalia creams, hair shampoos and conditioners, hair styling products, and face and body cleansers.

DEG is included on the List of Prohibited and Restricted Cosmetic Ingredients (more commonly referred to as the Cosmetic Ingredient Hotlist or simply the Hotlist), an administrative tool that Health Canada uses to communicate to manufacturers and others that products containing certain substances, when present in a cosmetic at certain concentrations, may contravene the general prohibition found in section 16 of the *Food and Drugs Act*, or may contravene one or more provisions of the *Cosmetic Regulations* (Health Canada [modified 2015]).

Use of EGBEA and monoglyme was not identified in cosmetics in Canada (personal communication, emails from the CPSD, Health Canada, to the ESRAB, Health Canada, dated September 2015; unreferenced).

<sup>16</sup> Natural health product types include, but are not limited to, acne therapy, counterirritant, medicated skin care, and sunscreen products

Based on the information above, exposures to DEG, TEG, DEGEE and DEGBE from use of selected product types was characterized. Dermal absorption values are presented in Table 7-1 and the estimates of dermal exposure for each substance are presented in Tables 7-2 and 7-3, respectively (see also Appendix A for the parameters used in the model developed for these scenarios).

**Table 7-2. Summary of estimates of dermal exposure of an adult to ethylene glycols and ethylene glycol ethers from use of cosmetics, natural health products, and over the counter drugs**

Substance (CAS RN)	Product scenario	Concentration (% w/w)	Estimated daily exposure (mg/kg bw/day)
DEG (111-46-6)	Antibacterial shampoo	3 <sup>a</sup>	0.027 (internal) <sup>b</sup> 0.054 (external) <sup>b</sup>
TEG (112-27-6)	Body cream	≤0.3 <sup>c</sup>	≤ 0.10 (internal) ≤ 0.20 (external)
DEGEE (111-90-0)	Deodorant/antiperspirant	10–30 <sup>c</sup>	0.55–1.7 (internal) 1.1–3.4 (external)
DEGEE (111-90-0)	Body cream	1–3 <sup>c</sup>	0.34–1.0 (internal) 0.68–2.0 (external)
DEGBE (112-34-5)	Facial makeup	10–30 <sup>c</sup>	0.47–1.4 (internal) 0.94–2.8 (external)

<sup>a</sup> Non-medicinal ingredient in antibacterial shampoo (personal communication, emails from the Health Products and Food Branch, Health Canada, to the Risk Management Bureau, Health Canada, dated October 2015; unreferenced).

<sup>b</sup> Estimates of external exposure are estimates of dermal deposition. Estimates of internal exposure are estimates of systemic exposure based on the dermal absorption values for each substance.

<sup>c</sup> Concentrations are based on notifications submitted under the *Cosmetic Regulations* to Health Canada (personal communication, emails from the CPSPD, Health Canada, to the ESRAB, Health Canada, dated September 2015; unreferenced).

**Table 7-3. Summary of estimates of acute dermal exposures of an adult to ethylene glycols and ethylene glycol ethers from use of cosmetics**

Substance (CAS RN)	Product scenario	Concentration (% w/w) <sup>a</sup>	Estimated per application exposure (mg/kg bw)
DEGEE (111-90-0)	Hair dye	3–10 <sup>b</sup>	4.2–14.0 (external) <sup>c</sup> 2.1–7.0 (internal)
DEGBE (112-34-5)	Hair dye	1–3	1.4–4.2 (external) 0.71–2.1 (internal)

<sup>a</sup> Concentrations are based on notifications submitted under the *Cosmetic Regulations* to Health Canada (personal communication, emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated September 2015; unreferenced).

<sup>b</sup> 97.5% of products contain 3-10% DEGEE; only 2.5% contain >10% (personal communication, emails from the CPSPD, Health Canada, to the ESRAB, Health Canada, dated September 2015; unreferenced).

<sup>c</sup> Estimates of external exposure are estimates of dermal deposition. Estimates of internal exposure are estimates of systemic exposure based on the dermal absorption values for each substance.

## Paint and coating products

In Canada, some of these substances are also used in paints and coatings (Environment Canada 2001; Environment Canada 2014). Globally, substances in this group may be present in a variety of paints and coatings, building products and do-it-yourself materials (Household Products Database 1993-2015; DOW 2007a, b; DOW 2014).

Dermal and inhalation exposures to substances in this group from use of waterborne roller wall paints and floor finish/sealers were estimated using ConsExpo v4.1 (ConsExpo 2006) and are presented in Table 7-4.<sup>17</sup> Scenarios were modelled to simulate the painting of either a wall or floor and include inhalation and incidental dermal routes (internal dermal estimates were derived using dermal absorption values from Table 7-1). No data were available for TTEG concentrations in paints; therefore, the concentration of TEG in paint was used as a surrogate for TTEG, and exposures are therefore expected to be similar.

**Table 7-4. Summary of estimates of dermal and air exposures of an adult to ethylene glycols and ethylene glycol ethers from use of paints and coatings**

Substance (CAS RN)	Product scenario <sup>a</sup>	Concentration (% w/w)	Estimated dermal exposure per application (mg/kg bw) <sup>b</sup>	Instantaneous mean event air concentration during use (mg/m <sup>3</sup> )
DEG (111-46-6)	Water-borne roller wall paints	1 <sup>c</sup>	0.254 internal; 0.51 external	0.27
TEG (112-27-6)	Water-borne roller wall paints	0.1–4% <sup>d</sup>	1.02 Internal; 2.04 external	0.25
TTEG (112-60-7)	Water-borne roller wall	0.1–4% <sup>d</sup>	1.02 Internal; 2.04 external	0.25

<sup>17</sup> The majority of floor/deck/wood sealants containing DEGEE and EGBEA are intended for professional use and have clear labeling regarding wearing personal protective equipment and ventilation. However, since some of these products are sold to the general public, exposure scenarios from use of these products were developed.

Substance (CAS RN)	Product scenario <sup>a</sup>	Concentration (% w/w)	Estimated dermal exposure per application (mg/kg bw) <sup>b</sup>	Instantaneous mean event air concentration during use (mg/m <sup>3</sup> )
	paints			
DEGEE (111-90-0)	Floor sealant	1–10 <sup>e</sup>	0.176 internal; 0.353 external	20.1
EGBEA (112-07-2)	Wood sealant	1–5 <sup>f</sup>	0.053 internal; 0.176 external	58.4
DEGBE (112-34-5)	Water-borne roller wall paints	2 <sup>g</sup>	0.51 internal; 1.02 external	0.5

<sup>a</sup> All scenarios conducted using ConsExpo (Health Canada 2016a; see also Appendix A).

<sup>b</sup> Estimates of external exposure are estimates of dermal deposition. Estimates of internal exposure are estimates of systemic exposure based on the dermal absorption values for each substance.

<sup>c</sup> MSDS 2012c

<sup>d</sup> Industry data submitted under section 71 of CEPA 1999 indicated that TEG is present in concentrations between the range of 0.1 to 4%. No data was available for TTEG concentrations in paints; however, industry submissions indicated a potential presence in paints and coatings. Therefore, the concentration of TEG in paint was used as a surrogate for TTEG and exposure is expected to be similar.

<sup>e</sup> MSDS 2012d.

<sup>f</sup> MSDS 2010d.

<sup>g</sup> MSDS 2015u.

The instantaneous mean event concentrations presented above may overestimate exposure as these substances have low to moderate vapour pressures (see Physical and Chemical Properties section).

### Painted toys mouthed by children

In Canada, some of these substances may be present in children's toys and articles (Environment Canada 2001; Environment Canada 2014); internationally, substances in this group have also been reported in painted toys (Hansen and Pederson 2005).

The Danish Ministry of the Environment reported migration of certain substances in this group from painted wooden toys into simulated saliva (Hansen and Pederson 2005). They analyzed all six of the substances in the EGs and EGEs subgroups, and four of the six substances (TEG, EGBEA, DEG, TTEG) were detected at low concentrations in simulated saliva from fewer than five products. Therefore, exposure to these four substances via this route is not expected to be significant.

Two of the substances (DEGEE and DEGBE) were detected in simulated saliva from four or more products (n=15) at moderate to high concentrations, and potential exposures to these substances via mouthing were estimated. The Danish Ministry of the Environment assessment of oral exposure from mouthing of toys was adopted for this

assessment and the highest reported oral uptakes for both substances are reported in Table 7-5.<sup>18</sup>

**Table 7-5. Estimated exposures to DEGEE and DEGBE from mouthing of a painted toy by children (Hansen and Pederson 2005)**

Substance (CAS RN)	Migration rate (ug/10cm <sup>2</sup> /h)	Highest oral uptake reported (ug/kg bw/day) <sup>a</sup>	Reference
DEGEE (111-90-0)	12.6	18.9	Hansen and Pederson 2005
DEGBE (112-34-5)	55.7	16.7	Hansen and Pederson 2005

<sup>a</sup> Absorption rate was assumed to be 100%, exposure for 3 hours, 10 kg body weight.

## Air fresheners

Spray-operated air fresheners containing concentrations of up to 1% DEG, up to 10% TEG and up to 30% DEGEE are sold in Canada (MSDS 2009b, 2014d, 2014e, Environment Canada 2009). Additionally, monoglyme may be found as a potential impurity (at concentrations < 0.01%, Environment Canada 2009) of EGEs used in air fresheners. However, it is not thought to be present in a widespread portion of products used by consumers.

Twenty-four hour mean event air concentrations from use of air fresheners containing DEGEE, TEG and monoglyme were estimated using ConsExpo v4.1 (ConsExpo 2006)<sup>19</sup> and are presented in Table 7-6 below. In addition, for monoglyme, a shorter duration mean event concentration (6 hours) matching the daily exposure duration of the critical study for risk characterization was also estimated.

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<sup>18</sup> Based on the same methodology and parameters for oral exposure from mouthing as those used in the State of the Science report for DINP<sup>18</sup> (Environment Canada and Health Canada 2015), the highest oral exposure for DEGEE and DEGBE would be 3.36 and 14.85 ug/kg bw/day, respectively. These oral uptake values are lower than those reported by the Danish Ministry of the Environment (Hansen and Pederson 2005).

<sup>19</sup> Parameters used in ConsExpo for this scenario were based on IFRA (2012) and internal consultations (see Appendix A).

**Table 7-6. 24-hour and 6-hour mean event air concentrations from air freshener use**

Substance (CAS RN)	Concentration (% w/w)	24-h (6-h) air concentrations
DEG (111-46-6)	1	0.187 mg/m <sup>3</sup>
TEG (112-27-6)	10	1.87 mg/m <sup>3</sup>
DEGEE (111-90-0)	30	5.62 mg/m <sup>3</sup>
Monoglyme (110-71-4)	0.01	0.0019 mg/m <sup>3</sup> (0.0073 mg/m <sup>3</sup> )

### Household cleaning products

In Canada, a majority of the EGEs have also been reported to be used in cleaning and disinfection products in the home and in professional settings such as hospitals and kitchens (Environment Canada 2001; Environment Canada 2014; personal communication, emails from the Health Products and Food Branch, Health Canada, to the Risk Management Bureau, Health Canada, dated October 2015; unreferenced). Globally, substances in this group may also be present in cleaning products including dish soaps, all purpose cleaners, and oven cleaners (Household Products Database 1993-2015).

Bathroom or all-purpose spray window cleaners containing concentrations of DEG, DEGEE, EGBEA, and DEGBE may be available in Canada (personal communication, emails from the Health Products and Food Branch, Health Canada, to the Risk Management Bureau, Health Canada, dated October 2015; unreferenced, MSDS 2013f; MSDS 2015v; OECD 2007). Twenty-four hour mean event concentrations and dermal exposure estimates (internal dermal estimates were derived using dermal absorption values from Table 7-1) were estimated using ConsExpo v4.1 (ConsExpo 2006) and are presented in Table 7-7 (see also Appendix A for the parameters used in ConsExp v4.1).

**Table 7-7. Estimated dermal exposure and air concentrations of Ethylene Glycol Ethers from use of household cleaning products**

Substance (CAS RN)	Product	Concentration (% w/w)	Estimated dermal exposure (mg/kg bw/event; mg/kg bw/day)	24-h mean event concentrations (mg/m <sup>3</sup> )
DEG (111-46-6)	Bathroom cleaner	4 <sup>a</sup>	0.10 internal; 0.20 external	2.92
DEGEE (111-90-0)	Window Cleaner	8 <sup>b</sup>	0.19 internal; 0.38 external	3.14
EGBEA (112-07-2)	Window Cleaner	5 <sup>c</sup>	0.070 internal; 0.23 external	1.96

DEGBE (112-34-5)	Bathroom Cleaner	10 <sup>d</sup>	0.26 internal; 0.52 external	7.31
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<sup>a</sup> Personal communication, emails from the Health Products and Food Branch, Health Canada, to the Risk Management Bureau, Health Canada, dated October 2015; unreferenced.

<sup>b</sup> OECD (2007: p. 61).

<sup>c</sup> MSDS (2015v).

<sup>d</sup> MSDS (2013f).

The 24-h mean event concentrations are comparable to reported peak air (10.8 mg/m<sup>3</sup>) and breathing zone (5.4 mg/m<sup>3</sup>) concentrations from the use of a bathroom spray cleaner containing DEGBE, measured by HERA (2005). However, the modelled concentrations outlined above are estimated over 24 hours (during and post use) and highlight the conservatism of this model for these specific set of substances.

### Other products

Exposures from products such as adhesives, batteries, and textiles were not assessed, as the sentinel products presented above (personal care products, paints and coatings, air fresheners, household cleaning products) are expected to account for inhalation and dermal exposures from other less frequently used products.

## 7.2 Health Effects Assessment

### 7.2.1 Health effects assessment of the Ethylene Glycols subgroup

The majority of the health effects information for this subgroup is based on the Organisation for Economic Co-operation and Development (OECD) Screening Information Data Set (SIDS) Initial Assessment Report for the ethylene glycol category and the specific glycols: diethylene glycol (DEG), triethylene glycol (TEG) and tetraethylene glycol (TTEG) (OECD 2009a, 2009b, 2009c, 2009d). The scientific literature for these documents was updated by the OECD sponsor country (Canada). More recent information, based on a search of published literature conducted from January 2003 to September 2015, identified new health effects studies and resulted in the use in this screening assessment of different critical endpoints than those stated in OECD (2009a).

### Substance-specific health effects data for risk characterization

The EGs subgroup includes di-, tri-, and tetra-ethylene glycols, and this section provides critical endpoints and corresponding effect levels for DEG, TEG and TTEG to be used for risk characterization, as cited directly from the OECD (2009a, 2009b, 2009c, 2009d) and more recent publications, if applicable.

## Diethylene glycol (DEG)

The toxicokinetics of DEG was summarized in OECD (2009b) as follows: “Based on studies in rats and/or dogs, the main metabolic pathway is oxidation via alcohol dehydrogenases and aldehyde dehydrogenases (ADH/ALD). DEG and its metabolites do not significantly accumulate in tissues. DEG is primarily eliminated in urine as DEG and 2-(hydroxyethoxy)acetic acid [HEAA] and is also eliminated as exhaled CO<sub>2</sub>. DEG is readily absorbed by the oral route, but dermal absorption is limited (9% based on a dose of 200 mg/kg bw in rats).”<sup>20</sup> Although not stated in OECD (2009a, 2009b), in another study conducted by DOW (1981), dermal absorption in rats was higher than 9% at a lower applied dose within 24-h post-dosing. These data are described in the “Exposure Assessment” section.

For DEG, a short-term oral study was conducted in rats via the oral route. Test animals were exposed to 0, 11, 46, 180 or 850 mg/kg bw/day in feed for 32 days. The no-observed adverse effect level (NOAEL) and lowest-observed adverse effect level (LOAEL) were 180 and 850 mg/kg bw/day, respectively, based on increased kidney weight. A short-term inhalation study was also conducted in rats exposed to 0, 530, 3000 or 5000 mg/m<sup>3</sup> DEG, for 6 h/day for 9 days. The no-observed effect concentration (NOEC) and lowest-observed effect concentration (LOEC) were 3000 and 5000 mg/m<sup>3</sup>, respectively, based on minor changes in hematological and clinical chemistry parameters (OECD 2009a, 2009b). No short-term dermal studies were identified for DEG.

Two subchronic repeated-dose oral studies were conducted in rats; these 13-week and 32-week studies are further described in the supporting document (Health Canada 2016a). Two chronic repeated-dose oral studies were conducted in rats. In one study, animals were exposed to 0, 1200, or 2300 mg/kg bw/day DEG in feed for 3 to 24 months. An oral LOAEL of 2300 mg/kg bw/day was determined based on observation of bladder stones in males at 24 months; the NOAEL was 1200 mg/kg bw/day. In the other study, in contrast, no effects were observed in rats exposed to 25 000 ppm (equivalent to 3500 mg/kg bw/day) in drinking water for 2 years. However, the 2-year drinking water study specifically analyzed incidence of tumours, hematology and organ weights, with no effects observed (OECD 2009b).

Details of an oral continuous breeding study conducted in mice and oral developmental toxicity studies using DEG in rats, mice and rabbits in OECD (2009b) are summarized in the supporting document (Health Canada 2016a).

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<sup>20</sup> This is based on 9% radioactivity recovered in the urine, feces and exhaled CO<sub>2</sub> of rats 0 to 72 h after dosing (OECD 2009b).



Short-term toxicity has also been observed in humans based on a case-control study of 63 children aged one month to 13 years who had been exposed to acetaminophen syrup contaminated with DEG. These children showed idiopathic anuria and severe oliguria for 24 h or more, with other effects sometimes noted (hepatitis, pancreatitis, and severe neurological manifestations) with a median of 6 days from first dose to onset. Based on 32 affected children and 17 control children with no renal failure, for which maximum ingested doses of DEG could be estimated, a median dose of 1500 mg/kg bw (range 246–4942 mg/kg bw) was determined as the probable effect level for renal failure in children aged one month to 13 years. The estimated ingestion of DEG in 17 control children (no renal failure) was 56 to 2773 mg/kg bw. Note that there is a large overlap in estimated toxic and non-toxic doses of DEG in children (O'Brien et al. 1998; OECD 2009b).

Additionally, there have been several epidemiology studies published since the OECD report and dossier (2009a, 2009b) were released. None of the more recent studies provided information on the point of departure selection for the human health risk assessment. A summary is provided in the supporting document (Health Canada 2016a).<sup>21</sup>

### **Triethylene glycol (TEG)**

The toxicokinetics of TEG was summarized in OECD (2009a, 2009c). Based on studies in rats and/or rabbits, the main TEG metabolic pathway is oxidation via ADH/ALD. TEG was primarily eliminated in urine as TEG and ethylenedioxydiacetic acid, and only 1% was degraded and eliminated as exhaled CO<sub>2</sub> (OECD 2009c; DOW 2016a). OECD (2009a, 2009c) did not provide a dermal absorption value for TEG. However, based on unpublished data for DEG submitted to Health Canada, TEG dermal absorption was considered to be 50% (see Section 7.1.2).

In a short-term oral study conducted in rats, animals were exposed to 0, 1132–1177, 2311–2411, or 5916–6209 mg/kg bw/day of TEG in feed for 14 days. The NOAEL and LOAEL were 1132 and 2311 mg/kg bw/day, respectively, based on a dose-related increase in urine volume (Ballantyne and Snellings 2007). No short-term dermal studies were identified for TEG. Two 9-day inhalation studies were conducted in rats, and an adverse effect level was determined in one of them. In this study, animals were exposed

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<sup>21</sup> One of the epidemiology studies estimated a lethal dose in 15 adults, which was a subsample of 29 people who died after ingesting propolis syrup containing 65% DEG (Ferrari and Giannuzzi 2005). The lethal dose estimated by the authors was corrected by Schep and Slaughter (2005). However, due to the small number of subjects and lack of control cases in this study, this lethal dose estimate cannot be validated.

nose-only to 0, 102, 517 or 1036 mg/m<sup>3</sup> for 6 h/day for 9 days. The no-observed adverse effect concentration (NOAEC) and lowest-observed adverse effect concentration (LOAEC) were 517 and 1036 mg/m<sup>3</sup>, respectively, based on decreased body-weight gains in both sexes (Ballantyne et al. 2006; OECD 2009a, 2009c).

A subchronic repeated-dose oral study was conducted in rats exposed to 0, 748–848, 1522–1699 or 3849–4360 mg/kg bw/day TEG in diet for 13 weeks. An oral NOAEL and LOAEL of 1522 and 3489 mg/kg bw/day, respectively, were determined based on decreased body weights in both sexes, altered urine values (decreased pH in both sexes, decreased urine volume in males) and slightly increased relative kidney weights (Ballantyne and Snellings 2007; OECD 2009c). In two inhalation studies conducted in monkeys for periods up to 13 months, no adverse effects were observed at concentrations up to 6.14 mg/m<sup>3</sup> (exposure duration/day not stated) (Ballantyne and Snellings 2007; US EPA 2005).

Summaries of chronic repeated-dose oral studies conducted in rats and monkeys, an oral continuous breeding study conducted in mice, and oral developmental toxicity studies using TEG in rats and mice are provided in the supporting document (2016a).

In humans, no literature documenting cases of oral ingestion of pure TEG were identified. For the few reported cases of ingestion, any interpretation of effects was complicated by the presence of other substances (Ballantyne and Snellings 2007).

### **Tetraethylene glycol (TTEG)**

*In vivo* toxicokinetic studies using TTEG were not identified. As stated in OECD (2009a, 2009d), TTEG may be assumed to be metabolized predominantly by ADH/ALD *in vivo*. Although OECD (2009a, 2009c) did not provide a dermal absorption value for TTEG, based on unpublished dermal data for DEG submitted to Health Canada, dermal absorption for TTEG was considered to be 50% (See Section 7.1.2).

For TTEG, three short-term oral studies were conducted in rats. Treatment-related effects were observed in only one of the three studies; increased volume and specific gravity of the urine in both sexes and decreased urinary pH in females at a dose of 4500 mg/kg bw/day in one of the two 28-day studies. The NOAEL in this study was 3380 mg/kg bw/day (Healing et al. 2016). The 14-day and two 28-day studies are described in the supporting document (Health Canada 2016a).

A subchronic repeated-dose dermal study was conducted in rats, in which animals were exposed to 0 or approximately 3360 mg/kg bw/day, for 6 h/day, 5 days/week for 13 weeks. This study was conducted according to OECD and U.S. Environmental Protection Agency (US EPA) guidelines and a wide range of parameters were examined. The NOAEL was 3360 mg/kg bw/day (OECD 2009d).

Though the available genotoxicity studies for DEG and TEG showed negative results, similar tests (*in vitro* chromosome aberration and sister chromatid exchange assays, *in vivo* assays for chromosome levels) conducted with TTEG have shown positive or equivocal results. However, based on the overall genotoxicity database and quantitative structure-activity relationship (QSAR) investigation of genotoxicity for TTEG, as well as two-year rat and/or mouse studies using DEG or ethylene glycol (EG), OECD (2009a) concluded that the members of the EG category [EG, DEG, TEG, TTEG, and pentaEG] were not regarded as carcinogens.

Although no standard reproductive toxicity studies or any developmental toxicity studies were identified for TTEG, OECD (2009a) concluded that TTEG showed a low potential for reproductive toxicity based on lack of histopathological changes in the testes and epididymides of rats administered TTEG for either 14 days or 4 weeks.

### **Read-across/analogue hazard data for risk characterization**

As noted above, because there was a lack of dermal absorption data for TEG and TTEG, DEG dermal absorption data (50%) was used to estimate dermal absorption for TEG and TTEG. There was also no inhalation toxicity data for TTEG. However, since these substances were evaluated as a group by the OECD (2009a), the inhalation data for TEG was considered as an appropriate analogue for TTEG. As stated in OECD (2009a), the data for five EG substances show that as the molecular weight increases above that of DEG in the homologous series, the potential for systemic, reproductive, and developmental toxicity decreases. This pattern is consistent with a likely decrease in absorption with increasing molecular weight, although available data for direct comparison were limited and inconclusive.

Although the only repeated-dose dermal study identified was a 13-week TTEG dermal study in rats, TTEG was not considered valid for read-across for dermal repeated dosing for DEG and TEG, as the rabbit dermal LD<sub>50</sub> increases from 12 500 mg/kg bw for DEG to 22 600 mg/kg bw for TTEG, and the oral toxicity database shows that the severity of toxicological effects decreases from DEG to TEG to TTEG at similar dose levels.<sup>22</sup> Thus, substance-specific oral studies with critical effect levels (LOAEL or NOAEL) for the substance in question (DEG or TEG) will be used as surrogates for dermal toxicity in risk characterization of these substances.

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<sup>22</sup> Rat oral LD<sub>50</sub> increases from 15 600–25 300 mg/kg bw for DEG to 32 800–34 700 mg/kg bw for TTEG; 14-day oral rat NOAEL = 1132 mg/kg bw/day for TEG vs. 6387 mg/kg bw/day for TTEG; no 14-day study was identified for DEG. For DEG, a 32-day oral study LOAEL = 850 mg/kg bw/day based on increased kidney weight vs. a 28-day LOAEL = 4500 mg/kg bw/day for TTEG based on increased volume and increased specific gravity of the urine in both sexes and decreased urinary pH in females; no 4-5 week study was identified for TEG.

In contrast, although acute and repeated-dose toxicity shows decreasing severity of toxicological effects from DEG to TEG to TTEG, this trend is not apparent for developmental toxicity, as shown in the supporting document (Health Canada 2016a).

## **7.2.2 Health effects assessment of the Ethylene Glycol Ethers subgroup**

Different international organizations (e.g., OECD and the European Chemicals Agency [ECHA]) analyzed and summarized the health effects information and characterized hazard for the Ethylene Glycol Ethers subgroup. Therefore, these documents are used to inform the health effects assessment for the respective substances, including selection of effect levels for critical endpoints and NOAELs/NOAECs.

### **Substance-specific health effects data for risk characterization**

This subgroup includes one monoethylene glycol acetate and two diethylene glycol ethers, and this section provides critical endpoints and corresponding effect levels for DEGEE, EGBEA and DEGBE, to be used for risk characterization.

#### **Diethylene glycol monoethyl ether (DEGEE)**

OECD (2007) and SCCP (2006a) summarize the health effects literature related to DEGEE. A literature search was conducted from the year prior to the OECD SIAM<sup>23</sup> (i.e., October 2004 to April 2016), and no health effects studies that would result in critical effect levels lower than those identified by OECD (2007) were identified.

Available animal metabolism studies for members of the diethylene glycol ether substances indicate that the principal route of elimination is via urine. Only low or trace amounts of metabolites are found in expired air or faeces. The two major urinary metabolites for DEGEE—ethoxyethoxyacetic acid and DEG—are excreted within the first 24 hours. Based on limited data, similar metabolism of DEGEE is expected in humans (OECD 2007).

Available *in vitro* and *in vivo* data suggest that DEGEE is not considered to be genotoxic. Two carcinogenicity studies for DEGEE reported no increases in tumoral responses; however, these studies had limitations. Further details of these studies are provided in the supporting document (Health Canada 2016a). The oral bioavailability of DEGEE in experimental animals is reported to be 79–95% (DOW 2016b).

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<sup>23</sup> OECD (2007) is the result of an OECD SIDS Initial Assessment Meeting (SIAM), specifically SIAM 21, which occurred on October 18-20, 2005.

DEGEE is of low inhalation acute toxicity given that at the maximum attainable vapour concentration (560 mg/m<sup>3</sup>), no rats died when exposed for 7 hours (OECD 2007).

In an oral short-term study, rats were exposed to 0, 1340, 2680 or 5360 mg/kg bw/day of DEGEE by gavage for 5 days/week for 6 weeks. Mortality was observed at the highest dose along with presence of bloody urine. At 2680 mg/kg bw/day, no significant effects were observed; however, relative liver, heart, and kidney weights (but not absolute weights of these organs) were also increased with respect to controls. Pathological changes included hyperkeratosis of the stomach and splenic congestion. The NOAEL for this study is 1340 mg/kg bw/day (Krasavage and Vlaovic 1982 as cited in OECD 2007).

In a 90-day oral study, pigs were administered 0, 167, 500 or 1500 mg/kg bw/day in the diet.<sup>24</sup> A wide variety of parameters, including body and organ weights, hematological and urinary parameters, and tissue histopathology, were examined. Hydropic degeneration of liver and kidney proximal tubules were observed in one of two females treated with 500 mg/kg bw/day and all animals treated with 1000–1500 mg/kg bw/day. The relative weight of kidneys was increased and red blood cell counts were also reduced in males treated with 1500 mg/kg bw/day. The NOAEL was determined to be 167 mg/kg bw/day (Gaunt et al. 1968 as cited in OECD 2007).

In a 28-day dermal study, rabbits were administered 0, 100, 300 or 1000 mg/kg bw/day of DEGEE. There were no treatment-related signs of gross toxicity, adverse health effects or abnormal behaviour. The NOEL for systemic toxicity is considered to be 1000 mg/kg bw/day (Gattefosse 1994 as cited in SCCP 2006a).

With respect to sub-chronic exposure, rabbits were dermally administered DEGEE (0, 99, 296, 986 or 2957 mg/kg bw/day) for 5 days/week for 12 weeks. Increased blood urea nitrogen levels and severe kidney injury were reported at 2957 mg/kg bw/day in 1 of 4 surviving animals. Moderate kidney changes in 3 of 4 surviving animals were observed at the 986 mg/kg bw/day dose level. Based on these effects, the NOAEL was determined to be 296 mg/kg bw/day. However, this study had low numbers of animals and limited information on specific effects and may therefore be of low reliability (Dow Chemical Company 1950, as cited in OECD 2007).

For DEGEE, a chronic oral drinking water study was conducted in rats over three generations (two groups each of 8/sex/dose: DEGEE with 29.5% ethylene glycol or DEGEE with less than 0.2% ethylene glycol - high purity). Groups were administered the equivalent of 0, 10, 40, 200 or 950 mg/kg bw/day of high or low purity DEGEE for up

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<sup>24</sup> Highest dose reduced to 1000 mg/kg bw/day after three weeks due to severe toxicity.

to 718 days. Only livers and kidneys were examined microscopically in all animals. Kidney damage and bladder concretions<sup>25</sup> were observed in 2 of 28 animals administered 950 mg/kg bw/day of high purity DEGEE. The NOAEL for high purity DEGEE was 200 mg/kg bw/day. The NOAEL for the low purity DEGEE was 10 mg/kg bw/day based on 4, 11, and 39% of rats with pathological changes at 40, 200 and 950 mg/kg bw/day, respectively. Although effects were not specified at 40 mg/kg bw/day, in secondary sources, kidney damage, bladder concretions and cloudy swelling in the livers were observed at 200 and 950 mg/kg bw/day (Smyth et al. 1964 as cited in SCCP 2006a; Smyth et al. 1944 as cited OECD 2007). No chronic or sub-chronic inhalation studies were identified for DEGEE.

Summaries of an oral mouse two-generation reproduction study and limited developmental toxicity studies in rats and mice, as well as summaries of a 28-day inhalation study conducted in rats and daily exposure of mice, rabbits, cats and guinea pigs subjected to a saturated air concentration of DEGEE, are provided in the supporting document (Health Canada 2016a).

Repeated-dose studies and reproductive/developmental toxicity studies conducted using DEGEE (administered up to 2 years) show that the target organs (when effects were observed) were kidney and liver.<sup>26</sup> Additionally, these effects were also observed in multiple species through different routes of exposure and at similar doses (between 1000–2700 mg/kg bw/day), indicating that systemic effects occur predominantly at doses greater than 1000 mg/kg bw/day.

### **Ethylene glycol monobutyl ether acetate (EGBEA)**

OECD (2006) and EC (2006-2008a) summarize the available health effects literature related to EGBEA, and a literature search conducted from the year prior to OECD (2006) (i.e., August 2005 to April 2016) did not identify new health effects information. Only limited data was available on inhalation toxicity and repeated-dose toxicity by the oral and dermal routes.

The inhalation LC<sub>50</sub> for EGBEA was greater than 2660 mg/m<sup>3</sup> in rats and rabbits (EC 2006-2008a). Repeated-dose inhalation studies showed signs of hematotoxicity and associated lesions in all species except guinea pigs at a concentration in air of 400 ppm = 2621 mg/m<sup>3</sup> (only concentration tested). However, these studies have significant

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<sup>25</sup> A calculus or hard inorganic mass in a natural cavity or in tissue.

<sup>26</sup> Other organs such as the spleen may also be affected.

limitations and were not considered by the European Commission to be reliable for risk assessment (EC 2006-2008a).

Available evidence demonstrates that EGBEA is rapidly hydrolyzed to EGBE (CAS RN 111-76-2) by esterases present in mammalian blood and other tissues (Environment Canada and Health Canada 2002a; OECD 2006).<sup>27</sup> Therefore, due to the limitations of the EGBEA studies and since EGBEA is rapidly hydrolyzed to EGBE, toxicity data for EGBE were used to characterize risk for EGBEA.

### **Read-across/analogue health effects data for risk characterization**

EC (2006-2008b) summarized the available health effects literature related to EGBE. A literature search was conducted from the year prior to EC (2006-2008b) (i.e., August 2007 to April 2016), and no additional health effects studies that would result in lower critical effect levels were identified.

EGBE had been previously classified as an International Agency for Research on Cancer (IARC) Group 3 substance (inadequate evidence of carcinogenicity in humans and limited evidence of carcinogenicity in animals). However, in 2004, IARC concluded that there was no significant evidence for human carcinogenicity and no longer classified this substance under Group 3 (EC 2006-2008b). *In vivo* and most *in vitro* genotoxicity assays suggest that EGBE is not considered to be genotoxic. However, some assays have shown positive or equivocal results (details provided in the supporting document; Health Canada 2016a).

Two studies were available to assess the short-term dermal toxicity of EGBE. In a 9-day study, signs of toxicity were recorded and were limited to transient signs of hemolysis on rabbits after a 9-day exposure to EGBE at 900 mg/kg bw/day (doses of 0, 45, 225, 450 or 900 mg/kg bw/day). This study NOAEL of 450 mg/kg bw/day was based on hematological effects (Bushy Run Research Center 1980 as cited in EC 2006-2008b). To assess immune system effects, EGBE was administered dermally to mice at 0, 100, 500, 1000 or 1500 mg/kg bw/day for 4 days. At the 1500 mg/kg bw/day dose, an increase in relative spleen weight and in splenic cellularity were observed. No decreases were observed in the proliferation of B cells whereas T lymphocytes exhibited a statistically significant decrease of proliferative responses at doses of 500

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<sup>27</sup> It is assumed that the rate of metabolism is close to 100% because OECD (2006) stated, "Since the acetates are absorbed to a similar extent as the glycol ethers and are rapidly hydrolyzed to their corresponding glycol ethers by esterases *in vivo*, the patterns of metabolic elimination for glycol ethers and their acetates should be nearly identical."

and 1000 mg/kg bw/day. In the mixed lymphocyte response assay, natural killer cells, cytotoxic T lymphocyte activity and T-dependent plaque-forming cell responses were unchanged after treatment. A NOAEL of 1000 mg/kg bw/day based on relative spleen weight increases at 1500 mg/kg bw/day was determined (Singh et al. 2001 as cited in EC 2006-2008b).

In a 13-week study, rabbits were treated dermally with 0, 10, 50 or 150 mg/kg bw/day, 5 days/week for 13 weeks. No effects were observed up to the highest dose tested of 150 mg/kg bw/day (Wil Research laboratories Inc. 1983 as cited in EC 2006-2008b).

In EGBE repeated-dose inhalation studies, the principal effect consistently observed was hemolysis, which was occasionally associated with secondary hepatic effects (Kupffer cells pigmentation and absolute and relative liver weight increases). The 1–3 week, 14-week, and 2-year studies in rats and the 2-year study in mice are further described in the supporting document. Inhalation developmental toxicity studies in rats and rabbits are also summarized in the supporting document (Health Canada 2016a).

In an oral gavage developmental toxicity study, pregnant female rats were dosed during gestation days (GD) 9 to 11 with 0, 30, 100 or 200 mg/kg bw/day of EGBE or during GD 11 to 13 with 0, 30, 100 or 300 mg/kg bw/day of EGBE. The maternal NOAEL and LOAEL were 30 and 100 mg/kg bw/day, respectively, based on decreased body weight and/or weight gain, increased kidney and spleen weights, and severe hematotoxicity typical of hemolytic anaemia. As stated in EC (2006-2008b), a developmental NOAEL and LOAEL of 100 and 200 mg/kg bw/day, respectively, were determined based on increased fetal lethality without malformations. However, these effects were observed only in the presence of maternal toxicity.

Another oral developmental study reported reproductive effects (decreased number of fertile females, decrease in litters/fertile pair) and maternal effects (increased female deaths, decreased body weights, etc.) at doses higher than reported above (EC 2006-2008b). See the supporting document for details (Health Canada 2016a).

Although the lowest effect levels for EGBE administration induce hemolytic toxicity in rodents, mechanistic and mode of action studies have shown that EGBE's metabolite, 2-butoxyacetic acid (BAA), is responsible for the hematoxicity in rodent species and that humans are 30 times less sensitive than rats to this hemotoxic effect (EC 2006-2008b). Complex mode of action analyses have also shown that human red blood cells are 40 to 150 less sensitive to hematoxicity than rat blood cells and that under different susceptibility conditions (physiological or blood diseases), humans are still resistant to the hemolytic toxicity of BAA (US EPA 2010). This is evident, as following high oral doses of EGBE (up to 4500 mg/kg bw/day) in humans, the main toxic effect was metabolic acidosis and central nervous system depression, accompanied with hematotoxicity (hematuria) in some cases (based on case reports in adult humans ingesting products containing 10–35% EGBE). The lowest acute dose leading to metabolic acidosis in humans was 400 mg/kg bw (LOAEL) (EC 2006-2008b).



## Diethylene glycol monobutyl ether (DEGBE)

EC (2000) summarizes the health effects literature related to DEGBE. A literature search was conducted from the year prior to finalization of the EC (2000) (i.e., July 1998 to April 2016). One study potentially relevant to the risk characterization was identified, and information on this study is provided below.

DEGBE is of low inhalation acute toxicity given that at the maximum attainable vapour concentration (120 mg/m<sup>3</sup> DEGBE), no rats died when exposed for 7 hours.

Available *in vitro* and *in vivo* data suggest that DEGBE is not considered to be mutagenic or genotoxic. Further details are provided in the supporting document (Health Canada 2016a).

The literature search identified a 2005 subchronic study in which DEGBE was administered to rats for 13 weeks at doses of 0, 50, 250 or 1000 mg/kg bw/day in drinking water (see Table 7-8 for details).

**Table 7-8. Updated critical endpoint values for DEGBE**

Endpoint	Study details	Critical effect level and health effect endpoint	Citation
Repeated-exposure; subchronic toxicity  (13 weeks)	Species: Rat (10/sex/dose)  Route: Oral (drinking water)  Concentration and Duration: 50, 250 or 1000 mg/kg bw/day for 13 weeks	<b>NOAEL = 250 mg/kg bw/day</b>  <b>LOAEL = 1000 mg/kg bw/day</b>  Changes in hematology and clinical chemistry parameters. Changes in organ weights of liver and kidney. Histopathological lesions in liver of females	Johnson et al. 2005

EC (2000) reported one 6-week oral gavage study and one 13-week oral gavage study in rats, but a NOAEL was not determined in either study. The 6-week study utilized high doses (891 to 3564 mg/kg bw/day), and although the 13-week study utilized lower doses (51 to 1630 mg/kg bw/day), it was considered of limited quality because the effects observed were not consistent with the known toxicity profile of glycol ethers (e.g., hyperkeratosis of the stomach, high unclarified mortality at the doses of 254 to 1630 mg/kg bw/day). Thus, the study by Johnson et al. (2005) described above (Table 7-8) is used in the risk characterization of oral exposures.

In a 13-week dermal study, rats were exposed to 0, 200, 600 or 2000 mg/kg bw/day of DEGBE for 5 days/week, 6 h/day (occluded). No mortality or effects on body weight,

organ weights, pathology or clinical chemistry were observed at any of the doses tested. DEGBE caused local effects, such as erythema, in all groups, and severity and time of onset were concentration dependent. The NOAEL for systemic effects was determined to be 2000 mg/kg bw/day (Auletta et al. 1993 as cited in EC 2000).

DEGBE is not considered harmful by inhalation, possibly due in part to its low vapour pressure and volatility (Patty 1994 as cited in EC 2000). This is confirmed by 2-week, 5-week, and 90-day inhalation studies conducted in rats, in which effects were observed at vapour concentrations  $\geq 100 \text{ mg/m}^3$  (effects on the lungs, spleen and liver observed in the 2- and 5-week studies; in the 90-day study, the NOAEC was established at  $94 \text{ mg/m}^3$ , the highest concentration tested). Details of these studies are provided in the supporting document (Health Canada 2016a).

In a dermal developmental study, pregnant female rabbits were administered 0, 100, 300 or 1000 mg/kg bw/day DEGBE, 4 hours a day, from gestation days (GD) 7 to 18 (12 days, non-occluded), and were sacrificed on GD 29. Maternal body weight gain was slightly decreased at the two higher dose levels but not statistically significant. The NOAEL for systemic toxicity is 1000 mg/kg bw/day (Nolen et al. 1985; EC 2000).

In another dermal study, pregnant rabbits were exposed to non-occluded DEGBE at doses of 0, 100, 300 or 1000 mg/kg bw/day for 4 h/day from GD 7 to 18. The developmental and maternal NOAEL was the highest dose tested, i.e. 1000 mg/kg bw/day (Nolen et al. 1985; EC 2000). In a one-generation dermal reproduction study conducted in rats, no reproductive or systemic toxicity was observed at the only dose tested, 2000 mg/kg bw/day (EC 2000).

A 30-day oral study and an oral one-generation reproduction study in rats, as well as an oral developmental toxicity study in mice are summarized in the supporting document (Health Canada 2016).

In the oral rat repeated-dose studies mentioned above, DEGBE showed hemolytic toxicity at doses  $\geq 250 \text{ mg/kg bw/day}$ . *In vitro* studies of putative metabolites of DEGBE have shown that human red blood cells are much less sensitive to hemotoxicity than rat blood cells (SCCP 2006b; OECD 2007). Humans are considered to be more resistant than rats to the hemolytic toxicity of DEGBE's metabolites (2-butoxyacetic acid, butoxyethoxyacetic acid) based on interpretation of the proposed metabolic pathway described in SCCP (2006b).

### **7.2.3 Health effects assessment of monoglyme**

Monoglyme is classified under Europe's harmonised classification and labelling system as a substance that may damage fertility and may damage the unborn child (Repr. 1B: H360FD). Under the European REACH program, it is classified as a substance that may damage fertility or the unborn child and is suspected of causing cancer (European Union 2016g).

ECHA (2012b) assessed monoglyme and selected the developmental and reproductive toxicity studies as the most robust and sensitive studies for dose-response analysis. NICNAS (2016a) was also used as supplementary information for monoglyme. Monoglyme metabolizes to 2-methoxyethanol (2-ME) and then to 2-methoxyacetic acid, and the toxicity of monoglyme is attributed to these two metabolites (ECHA 2012b; NICNAS 2016a). No toxicokinetic studies were identified for monoglyme, but based on NICNAS (2016a) and ECHA (2012b), monoglyme and diglyme (CAS No. 111-96-6), of which the toxicokinetics have been studied, are considered to be metabolized by the same enzymatic metabolic pathway and demonstrated similarity of metabolic products such as 2-ME and 2-methoxyacetic acid, with only 2% of the administered dose remaining in the carcass of mice. 2-ME was previously assessed by Environment Canada and Health Canada (2002b), and relevant data are discussed under “Read-across/analogue hazard data for risk characterization.”

The potential health effects associated with monoglyme are based on the results of repeated-dose (effects on blood, thymus, adrenal gland, and testicular degeneration) and developmental (increased fetal death and skeletal effects and decreased fetal body weight) toxicity studies at relatively low doses. Available *in vitro* data also suggest that monoglyme is not genotoxic; however, no *in vivo* genotoxicity data were available (NICNAS 2016a).

Monoglyme has low acute oral and dermal toxicity ( $LD_{50} > 2000$  mg/kg bw in rabbits) and has low to moderate acute toxicity via the inhalation route ( $LC_{50}$  between 20 and 63 mg/m<sup>3</sup>). No repeated-dose toxicity data were identified via the oral or dermal route for monoglyme.

In a repeated-dose inhalation study, rats were exposed by whole-body inhalation to monoglyme vapours for 6 h/day, 5 days/week for 2 weeks. The NOAEC and LOAEC for this study were 50 and 250 ppm (187 and 935 mg/m<sup>3</sup>), respectively, based on reversible reduction of cell layers of seminiferous epithelium in male rats. In contrast, in a similar study using rabbits exposed by whole-body inhalation, irreversible changes to the seminiferous epithelium of the testes occurred at 935 mg/m<sup>3</sup> (ECHA 1986a, 1986b, 2012a, 2012b).

In a developmental study, pregnant female rats were exposed by oral gavage to monoglyme during GD 8 to 18. At doses of greater than 120 mg/kg bw/day, 100% fetal death was observed. At doses of 30 or 60 mg/kg bw/day, fetotoxic effects were also observed; therefore, a LOAEL of 30 mg/kg bw/day based on increased frequency of stillborn pups, fetal edema, and increased gestation length was derived. A maternal NOAEL of 60 mg/kg bw/day was determined based on decreased body weight gains (partly due to early deaths) at doses of 120 to 1000 mg/kg bw/day (Leonhardt et al. 1991 as cited in ECHA 2012b).

In an earlier developmental toxicity study, pregnant female rats were exposed to monoglyme via inhalation (whole body) for 6 h/day during GD 7 to 16 (10 days). Fetal

resorptions along with delayed ossification and other fetal effects (fragmented thoracic and lumbar vertebrae, malformations of ribs, enlarged ureter, blood in the pericardium, etc.) were observed at 32 and 100 ppm (120 and 374 mg/m<sup>3</sup>). Fetal death and other fetal effects (malformations of extremities, body weight decreases, etc.) were observed at the highest dose of 100 ppm (374 mg/m<sup>3</sup>). The NOAEC and LOAEC for developmental toxicity were determined to be 10 and 32 ppm (37 and 120 mg/m<sup>3</sup>), respectively, based on retarded development and increased incidence of malformations. A maternal NOAEC of 100 ppm (374 mg/m<sup>3</sup>) was also determined (Supporting Study 1986 as cited in ECHA 2012b). In a similar study conducted at the same time, pregnant rabbits were exposed to monoglyme via inhalation (whole body) for 6 h/day during GD 6 to 18 (13 days), followed by a recovery period of 10 days. At the highest dose of 50 ppm (187 mg/m<sup>3</sup>), vitality of the litters within the first 24 hours after Caesarean section was considerably decreased and fetal anomalies were noted in several fetuses (abnormal orientation of fore-paws, skull malformations and ossification irregularities, red-bordered spots on skin). A developmental NOAEC and LOAEC of 16 and 50 ppm (60 and 187 mg/m<sup>3</sup>), respectively, were determined based on the decreased vitality in pups and the fetal anomalies. The maternal NOAEC and LOAEC was also 16 and 50 ppm (60 and 187 mg/m<sup>3</sup>), respectively, based on slightly decreased food consumption at both of these concentrations (ECHA 1988a, 1988b; ECHA 2012b). Although this inhalation study in rabbits suggests that fetal effects were seen at the same doses as maternal effects, note that in the rat inhalation study, fetal effects (increased incidence of malformations and delayed ossification) were observed at 120 mg/m<sup>3</sup> in the absence of maternal toxicity.

### **Read-across/analogue health effects data for risk characterization**

As noted above, monoglyme metabolizes to 2-ME and then to 2-methoxyacetic acid, and its toxicity is attributed to these two metabolites (ECHA 2012b; NICNAS 2016a). This supports the use of 2-ME as an analogue for assessing the toxicity of monoglyme. Based on similar arguments, a submission to the US EPA by Ferro Corporation (2002) also supported the use of 2-ME as an analogue.<sup>28</sup> 2-ME was previously assessed by Environment Canada and Health Canada (2002b) and NICNAS (2016b).

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<sup>28</sup> Ferro Corporation (2002) stated although the relative pharmacokinetics of metabolism between monoglyme and 2-ME are speculative, "...information about the metabolic pathways and nearly identical developmental effects at similar dose levels indicates that the repeated-dose, reproductive, and developmental toxicity of Monoglyme can be ascertained from the results of these studies on 2-ME in the appropriate protocol."

As cited in NICNAS (2016b), 2-ME and other chemicals in the alkoxyethanols and acetates grouping<sup>29</sup> are well absorbed by all routes of exposure. Uptake through the exposed skin is considered to be a significant source of exposure in humans exposed to vapours. Once absorbed, these chemicals are distributed throughout the body, including the developing fetus. This may potentially result in levels of metabolites that are greater in the fetus than those observed in pregnant women.<sup>30</sup> The alkoxyethanols and acetates are extensively metabolized, with the majority excreted in the urine.

2-ME is not mutagenic *in vitro* but there is evidence that it may be clastogenic, and there is consistent evidence that the initial metabolite, 2-methoxyacetaldehyde, is genotoxic in several cell lines. Likewise, the main metabolite, 2-methoxyacetic acid, was not mutagenic *in vitro*, but gave mostly positive results for clastogenicity in different assays. *In vivo* studies suggest that 2-ME is not genotoxic in somatic cells, but there is evidence that it causes genetic damage to male germ cells in rats at doses higher than 500 mg/kg bw/day (Environment Canada and Health Canada 2002b).

A number of repeated-dose toxicity studies on the metabolite, 2-ME, are available. 2-ME has been shown to cause adverse effects to the male reproductive system in a number of species by all routes of exposure. Effects on the female reproductive system have also been reported (changes in the oestrus cycle and hormone levels along with histopathological changes in the ovaries) (Environment Canada and Health Canada 2002b). Details of a 13-week rat drinking water study, a 28-day rat dermal study, a 13-week guinea pig dermal study, and 13-week inhalation studies in rats and rabbits are described in the supporting document (Health Canada 2016a). In the two 13-week inhalation studies conducted in rats and rabbits, a LOAEC of 93 mg/m<sup>3</sup> was determined in the rabbit study based on testicular effects (dose-related degeneration of the testes and testicular weight), whereas in the rat study, a LOAEC for degenerative effects on the testes was 933 mg/m<sup>3</sup>, but the overall NOAEC and LOAEC were 93 and 311 mg/m<sup>3</sup>, respectively, based on decreased body weights in females (Miller et al. 1983; Environment Canada and Health Canada 2002b). These studies show that the rabbit was more sensitive than rats to the testicular toxicity of 2-ME.

As shown below, 2-ME causes adverse developmental effects in the absence of maternal toxicity in a number of species by all routes of exposure. Developmental

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<sup>29</sup> In addition to 2-ME, the other chemicals in this grouping are 2-methoxyethanol acetate (CAS RN 110-49-6), 2-ethoxyethanol (CAS RN 110-80-5), and 2-ethoxyethanol acetate (CAS RN 111-15-9).

<sup>30</sup> This could be the case if the metabolites are preferentially retained in the fetus, since metabolism in the fetus is considered to be not as well developed as in the mothers.

effects were generally observed at doses lower than those observed for both reproductive and hematological effects. Also, the rabbit was more sensitive than rodent species to the developmental toxicity of 2-ME (Environment Canada and Health Canada 2002b).

In a developmental toxicity study, pregnant female rabbits were exposed daily via inhalation (whole body) during GD 6 to 18 (13 days) and sacrificed on GD 29. Significant teratologic effects (external, visceral and skeletal malformations) and decreased fetal body weight were observed at 156 mg/m<sup>3</sup>. Skeletal variations (delayed ossification of the sternebrae) were significantly increased in fetuses of animals exposed at 31 and 156 mg/m<sup>3</sup>. The NOEC and LOEC for delayed ossification were 9 and 31 mg/m<sup>3</sup> respectively, in rabbits. The LOAEC, based on fetal malformations, was 156 mg/m<sup>3</sup> (Hanley et al. 1984a, 1984b; Environment Canada and Health Canada 2002b).

Hanley et al. (1984a, 1984b) also conducted inhalation developmental toxicity studies in rats and mice using the same concentrations of 2-ME as those used in the rabbit study. In the rat study (pregnant females exposed whole body), an increase in skeletal variations (lumbar spurs and delayed ossification of the vertebrae) was observed in fetuses of animals exposed to 156 mg/m<sup>3</sup>. In the mouse study (pregnant females exposed whole body), an increase in testicular hypoplasia and skeletal variations (extra lumbar ribs) were observed in fetuses of animals exposed to 156 mg/m<sup>3</sup>. Transient decreases in maternal body weight gain among rats, mice and rabbits exposed at the highest dose (156 mg/m<sup>3</sup>) were the only consistent signs of maternal effects (Hanley et al. 1984a, 1984b; Environment Canada and Health Canada 2002b).

In a study conducted by Nelson et al. (1984), male rats were exposed to 0 or 78 mg/m<sup>3</sup> of 2-ME, 7 h/day, 7 days/week for 6 weeks, while pregnant female rats were exposed on GD 7 to 13 or 14 to 20. Exposed males were then mated with unexposed females and all groups of females were allowed to deliver normally. Selected groups of pups/litter were subjected to neuromotor behavioural tests and neurochemical studies of their brains. No signs of toxicity were observed in exposed male or female parents. In the pups of rats exposed to 78 mg/m<sup>3</sup>, neurochemical changes (significant differences in levels of acetylcholine, dopamine, norepinephrine and 5-hydroxytryptamine in the brains of 21-day old pups) and behavioural effects were observed (Environment Canada and Health Canada 2002b).

The inhalation developmental toxicity studies above indicate a LOEC of 31 mg/m<sup>3</sup> (and corresponding NOEC of 9 mg/m<sup>3</sup>) for increased incidence of skeletal variations in fetuses of rabbits, which is also stated in Environment Canada and Health Canada (2002b). This increased incidence of skeletal variations occurred in the absence of maternal toxicity. Increased incidences of skeletal variations were observed at 156 mg/m<sup>3</sup> in the rat and mouse inhalation developmental toxicity studies, not at 31 mg/m<sup>3</sup>. In terms of fetal malformations, increased incidences of this effect were observed at 156 mg/m<sup>3</sup> in both rabbits and mice. Although 2-ME did not appear to increase the incidence

of fetal malformations at 156 mg/m<sup>3</sup> in rats, note that in an independent monoglyme inhalation developmental toxicity study, an increased incidence of malformations (enlarged ureter and skeletal malformations) and delayed ossification was observed at 120 mg/m<sup>3</sup> in rat fetuses. These effects occurred in the absence of maternal toxicity.

The inhalation developmental toxicity studies were based on protocols of exposing the pregnant females to the substance for 6 h/day for 10 or 13 days during gestation. However, as shown above, effects were also observed in pups of female rats exposed to a single concentration of 2-ME over a shorter dosing period, i.e., for 7 days for 7 h/day, at a concentration of 78 mg/m<sup>3</sup>. Although gross necropsy or histopathological parameters were not examined in this study, the limited information suggests that short in utero fetal exposure during gestation (7 days) may result in neurochemical brain effects.

### **Human studies - 2-ME**

Effects on blood, bone marrow and sperm have been observed in workers exposed to 2-ME via inhalation or dermal contact. These effects include increased prevalence of anaemia, increased incidence of leukopenia, and hypoplasia of the bone marrow. Data were also available that indicate an association between exposures to the chemicals and adverse reproductive or developmental effects, including decreased sperm production, changes in sperm morphology, spontaneous abortion and congenital malformations. While confounding factors such as exposure to other chemicals cannot be ruled out (all of the populations studied were also exposed to other glycol ether solvents), these observations are consistent with those in experimental animals (Environment Canada and Health Canada 2002b).

## **7.3 Characterization of Risk to Human Health**

### **7.3.1 Characterization of risk to human health for the Ethylene Glycols subgroup**

As noted in section 7.1, environmental media and food are not expected to be significant sources of exposure for this subgroup. Exposure is expected to occur mainly from paints and coatings, personal care products, air fresheners, and household cleaning products. Available dermal or inhalation studies, though limited, were used to characterize risk where possible. However, oral short-term and subchronic critical effect levels were also used to characterize dermal risk.

The tables below provide all relevant exposure (highest exposure products from different routes and durations) and critical effect values for the EGs subgroup, as well as resulting margins of exposure (MOEs).

**Table 7-9. Relevant exposure and hazard values for DEG and resulting MOEs**

<b>Exposure scenario</b>	<b>Exposure concentration</b>	<b>Critical effect level</b>	<b>Critical hazard endpoint</b>	<b>Margin of exposure (MOE)</b>
Acute dermal exposure via waterborne roller paint	Acute dermal exposure (internal) = 0.25 mg/kg bw	NOAEL = 180 mg/kg bw/day based on 32-day feeding study in rats	Increased kidney weight in rats at 850 mg/kg bw/day	720
Daily dermal exposure via antibacterial shampoo	Daily dermal internal exposure = 0.027 mg/kg bw/day	NOAEL = 1200 mg/kg bw/day based on 90 day to 2 year feeding study in rats	Bladder stones in male rats at 2300 mg/kg bw/day	44 450
Inhalation acute exposure to 1% DEG in waterborne roller paint	Acute inhalation exposure = 0.269 mg/m <sup>3</sup>	NOAEC = 3000 mg/m <sup>3</sup> (9-day rat inhalation study)	Changes in hematology and clinical chemistry parameters in rats at 5000 mg/m <sup>3</sup>	11 150
24 hour mean event concentrations via bathroom cleaner	24 hour mean event concentration = 2.92 mg/m <sup>3</sup>	NOAEC = 3000 mg/m <sup>3</sup> based on 9-day rat inhalation study	Changes in hematology and clinical chemistry parameters in rats at 5000 mg/m <sup>3</sup>	1000

**Table 7-10. Relevant exposure and hazard values for TEG and resulting MOEs**

<b>Exposure scenario</b>	<b>Exposure concentration</b>	<b>Critical effect level</b>	<b>Critical hazard endpoint</b>	<b>Margin of exposure (MOE)</b>
Acute dermal exposure via waterborne roller paint <sup>a</sup>	Acute dermal exposure (internal) = 1.02 mg/kg bw	NOAEL = 1132 mg/kg bw/day TEG based on 14-day feeding study in rats	Dose-related increase in urine volume in rats at 2311 mg/kg bw/day	1110
Acute inhalation	Acute inhalation	NOAEC = 517 mg/m <sup>3</sup> TEG	Decreased body-weight	1920



Exposure scenario	Exposure concentration	Critical effect level	Critical hazard endpoint	Margin of exposure (MOE)
exposure via waterborne roller paint	exposure = 0.269 mg/m <sup>3</sup>	based on 9-day inhalation study in rats	gain in rats at 1036 mg/m <sup>3</sup>	
Daily dermal exposure via body cream	Daily dermal internal exposure = 0.1 mg/kg bw/day	NOAEL = 1522 mg/kg bw/day based on 13-wk feeding study in rats	Decreased body-weights decreased urine pH and increased kidney weights in rats at 3489 mg/kg bw/day.	15 220
24 hour mean event concentrations via air freshener (spray)	1.87 mg/m <sup>3</sup>	NOAEC = 517 mg/m <sup>3</sup> based on 9-day inhalation study in rats	Decreased body-weight gain in rats at 1036 mg/m <sup>3</sup>	280

**Table 7-11. Relevant exposure and hazard values for TTEG and resulting MOEs**

Exposure scenario	Exposure concentration	Critical effect level	Critical hazard endpoint	Margin of exposure (MOE)
Dermal acute exposure via waterborne roller paint <sup>a</sup>	Acute dermal exposure (internal) = 1.02 mg/kg bw	NOAEL = 3380 mg/kg bw/day TTEG based on 28-day drinking water study in rats	Increased urine volume and specific gravity and decreased urine pH in rats at 4500 mg/kg bw/day	3310
Inhalation acute exposure via waterborne roller paint <sup>a</sup>	Acute inhalation exposure = 0.269 mg/m <sup>3</sup>	NOAEC = 517 mg/m <sup>3</sup> TEG <sup>b</sup> based on 9-day inhalation study in rats	Read-across from TEG LOAEC in rats	1920

<sup>a</sup> Using TEG max concentration (4 %) as a surrogate.<sup>b</sup> The 9-day inhalation study in rats and the 13-week oral study in rats, using TEG, were also used as a surrogate to help determine risk to TTEG from inhalation exposures to paints and coatings.

The MOEs listed above are considered adequate to account for uncertainties in the health effects and exposure databases.

For the paint scenario (see Tables 7-9 to 7-11), a comparison between relevant NOAELs and NOAECs and the estimates of dermal and inhalation exposure results in MOEs of approximately 720 to 11 150 for the subgroup. For DEG, based on a human case-control study, a median dose of 1500 mg/kg bw was determined for children (6 months to 13 years) who experienced renal failure, which is higher than the LOAEL of 850 mg/kg bw/day determined from the 32-day oral rat study used in the paint scenario. This additional data supports MOEs based on experimental animal data as being protective of human health for this acute consumer product scenario.

For personal care products (i.e., body cream and antibacterial shampoo; see Tables 7-9 and 7-10), a comparison between relevant NOAELs and estimates of dermal exposure results in MOEs of 15 220 to 44 450 for the subgroup. For household cleaning products (i.e., air freshener and bathroom cleaner; see Tables 7-9 and 7-10), comparison between relevant NOAECs and the estimates of inhalation exposure results in MOEs of 280 to 1000 for the subgroup. A MOE of 280 was determined for the acute air freshener scenario using TEG when the 24-h mean event concentration was compared to the NOAEC of 517 mg/m<sup>3</sup> in a 9-day nose-only exposure inhalation study in rats. Note that this study was based on nose-only exposure for 6 h/day, and that effects were observed at a concentration twice that of the NOAEC (1036 mg/m<sup>3</sup>, decreased body-weight gain).<sup>31</sup> This inhalation NOAEC from exposures over 9 days when compared to the mean event concentration of 1.87 mg/m<sup>3</sup> (based on the maximum concentration of TEG in air fresheners), results in a conservative and protective MOE.

For all other products and exposure scenarios investigated, the MOEs determined were greater than those presented in the risk characterization tables above and thus are considered adequate to account for uncertainties in the health effects and exposure databases.

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<sup>31</sup> As shown in section 7.2.1, inhalation studies in monkeys for periods of up to 13 months showed no adverse effects at concentrations up to 6.14 mg/m<sup>3</sup>, but the exposure duration/day was not stated.

### 7.3.2 Characterization of risk to human health for the Ethylene Glycol Ethers subgroup

As mentioned in section 7.1, environmental media and food are not expected to be significant sources of exposure for this subgroup. Exposure is expected to occur mainly from personal care products, do it yourself products (i.e. floor sealant, waterborne roller paint) and household cleaning products. Exposure from the mouthing of toys was also considered in the risk characterization. Oral, dermal or inhalation studies, where available, were used to characterize risk. For dermal exposure, oral studies were also used to characterize risk in certain instances.

The tables below provide all relevant exposures (highest exposure products from different routes and durations) and hazard values for the EGEs subgroup, as well as resulting MOEs, for determination of risk.

**Table 7-12. Relevant exposure and hazard values for DEGEE and resulting MOEs**

<b>Exposure scenario</b>	<b>Exposure concentration</b>	<b>Critical effect level</b>	<b>Critical hazard endpoint</b>	<b>Margin of exposure (MOE)</b>
Daily oral exposure via mouthing of painted toy	0.0189 mg/kg bw/day	NOAEL = 167 mg/kg bw/day (90-day oral study in pigs)	Liver and kidney effects in female pigs at 500 mg/kg bw/day	8840
Acute dermal exposure via hair dye	4.2-14.0 mg/kg bw (external exposure)	NOEL = 1000 mg/kg bw/day (28-day dermal study in rabbits)	No effects	No MOE was determined.
	2.1–7.0 mg/kg bw/day (internal exposure)	NOAEL = 1340 mg/kg bw/day (6-week oral study in rats)	Limited pathological changes and organ weights changes at 2680 mg/kg bw/day	191–638
Daily dermal exposure via deodorant/ anti-	1.1–3.4 mg/kg bw/day (external exposure)	NOAEL = 296 mg/kg bw/day (12-week dermal study in rabbits)	Liver and kidney effects at 986 mg/kg bw/day.	87–269

<b>Exposure scenario</b>	<b>Exposure concentration</b>	<b>Critical effect level</b>	<b>Critical hazard endpoint</b>	<b>Margin of exposure (MOE)</b>
perspirant	0.55–1.7 mg/kg bw/day (internal exposure)	NOAEL = 200 mg/kg bw/day (2-year oral study in rats)	Kidney and bladder effects at 950 mg/kg bw/day	118–364

**Table 7-13. Relevant exposure and hazard values for EGBEA and resulting MOEs**

<b>Exposure scenario</b>	<b>Exposure concentration</b>	<b>Critical effect level</b>	<b>Critical hazard endpoint</b>	<b>Margin of exposure (MOE)</b>
Acute dermal exposure via window cleaner	0.23 mg/kg bw (external dermal exposure of EGBEA)	NOAEL = 1000 mg/kg bw/day (4-day dermal study in mice with EGBE)	Relative spleen weight increase at 1500 mg/kg bw/day.	4350
	0.07 mg/kg bw (internal exposure of EGBEA)	Maternal NOAEL = 30 mg/kg bw/day (Oral developmental toxicity study; rat dams dosed during three GD with EGBE)	Decreased body weight and/or weight gain, increased kidney and spleen weights, and severe hematotoxicity in dams at 100 mg/kg bw/day	429

**Table 7-14. Relevant exposure and hazard values for DEGBE and resulting MOEs**

<b>Exposure scenario</b>	<b>Exposure concentration</b>	<b>Critical effect level</b>	<b>Critical hazard endpoint</b>	<b>Margin of exposure (MOE)</b>
Daily oral exposure via mouthing of toy	0.0167 mg/kg bw/day	NOAEL = 250 mg/kg bw/day (13-week oral study in rats)	Liver and kidney effects at 1000 mg/kg bw/day	14 970

<b>Exposure scenario</b>	<b>Exposure concentration</b>	<b>Critical effect level</b>	<b>Critical hazard endpoint</b>	<b>Margin of exposure (MOE)</b>
Acute dermal exposure via hair dye	4.2 mg/kg bw/day (external exposure)	NOAEL = 1000 mg/kg bw/day (12-day developmental dermal study in rabbits)	No effects	238
Daily dermal exposure via facial makeup	2.8 mg/kg bw/day (external exposure)	NOAEL = 2000 mg/kg bw/day (13-week dermal study in rats)	No effects	714

For the toy scenario (see Tables 7-12 and 7-14), a comparison between relevant NOAELs and the highest oral exposure estimates results in MOEs of approximately 8840 to 14 970 for the subgroup.

For the personal care product scenarios (i.e., hair dye, antiperspirant/deodorant and facial makeup; see Tables 7-12 and 7-14), a comparison between relevant NOAELs and the estimates of dermal exposure results in MOEs of 87 to 714 for this subgroup. MOEs below 100 applied to products containing DEGEE only. However, these MOEs are considered acceptable for three reasons: 1) the dermal and oral studies used for the daily deodorant/antiperspirant scenario both showed effects at doses close to 1000 mg/kg bw/day, indicating that the MOEs based on much lower NOAELs identified for both studies (200 and 296 mg/kg bw/day) are conservative; 2) as stated in the “Health Effects” section, systemic effects observed in multiple species through different routes of exposure occur predominantly at doses greater than the limit dose of 1000 mg/kg bw/day of DEGEE; and 3) for the acute dermal hair dye scenario, the NOEL of 1000 mg/kg bw/day in the short-term dermal rabbit study was the highest dose tested, i.e. the limit dose, and thus, a NOAEL was not determined for acute dermal exposure. When this scenario considered using data from a short-term oral rat study and internal exposures that accounted for dermal absorption, the MOE was  $\geq 191$ . Therefore, the evidence indicates that acute and daily dermal risk is low for DEGEE.

For household cleaning products (see Table 7-13), a comparison between relevant NOAELs and the estimates of dermal exposure results in MOEs of 429 to 4350 for EGBEA.

All other products and scenarios resulted in acceptable MOEs that were larger than MOEs (comparable by exposure duration and route) presented in the risk characterization tables above.

With respect to the modelled air concentrations and inhalation exposures, bathroom cleaners, window cleaners and floor sealants are used infrequently and have clear guidelines regarding labelling (especially floor sealants).

Additionally, as mentioned in the “Exposure Assessment” section, measured peak air concentrations (right after bathroom cleaner use) are comparable to modelled 24-hour mean event concentrations, indicating the conservativeness of the ConsExpo inhalation model for this specific set of substances. However, EGEs are not considered harmful by inhalation, due in part to their low volatility and vapour pressure (Patty 1994 as cited in EC 2000). In addition, no adverse effects were observed in acute studies, and limited effects observed in longer duration studies also support low toxicity for DEGEE and DEGBE at maximal attainable vapour concentrations. For EGBE (the metabolite of EGBEA), carcinogenicity was observed in mice at the maximal attainable vapour concentration of 1208 mg/m<sup>3</sup> after 2 years of exposure (NOAEC: 604 mg/m<sup>3</sup>), while developmental and maternal effects were observed at 483 mg/m<sup>3</sup> (NOAEC: 242 mg/m<sup>3</sup>). There is a low likelihood that the general population would be exposed to the maximal attainable vapour concentration over an extended period of time. Therefore, given the above considerations, risk from inhalation is expected to be low and MOEs were not quantified for these products.

Therefore, all exposures presented above are considered to have MOEs that are adequate to address the uncertainties in the health effects and exposure databases.

### **7.3.3. Characterization of risk to human health for Monoglyme**

As cited in ECHA (2012b), the reproductive toxicity of monoglyme is considered to occur through its sequential metabolism to 2-ME and then to 2-methoxyacetic acid.

As noted in section 7.1, indoor air and the use of air fresheners are the major sources of exposure. The tables below provide all relevant exposures (highest exposure products from different routes and durations) and hazard values for monoglyme and 2-ME, as well as resulting MOEs, for risk characterization.

As noted in section 7.2.3, delayed ossification was observed after administration of 2-ME in fetuses of rabbits at a dose of 31 mg/m<sup>3</sup>. In contrast, fetal malformations were observed after administration of monoglyme and 2-ME in rats, mice and rabbits at a higher dose range of 120-156 mg/m<sup>3</sup>. Given that delayed ossification (at the lower dose)

was only observed in rabbits and that malformations were observed in three species (at higher doses), MOEs were determined for both effects.

**Table 7-15. Relevant exposure and hazard values for monoglyme and its metabolite 2-ME, as well as resulting MOEs**

Exposure scenario	Exposure concentration	Critical effect level	Critical hazard endpoint	MOE
Indoor air	0.013 mg/m <sup>3</sup> (monoglyme)	NOEC = 9 mg/m <sup>3</sup> (2-ME) $\approx$ 10.7 mg/m <sup>3</sup> (monoglyme)	Skeletal variations (delayed ossification of the sternebrae) in fetuses at 31 mg/m <sup>3</sup> in a rabbit developmental toxicity study	823
		NOAEC = 37 mg/m <sup>3</sup> (monoglyme) <sup>a</sup>	Skeletal and visceral fetal malformations at 120 mg/m <sup>3</sup> in a rat developmental toxicity study	2850

<sup>a</sup> **Note:** Fetal malformations were observed at 156 mg/m<sup>3</sup> after 2-ME administration. On a molar basis, 31 mg/m<sup>3</sup> 2-ME is the same as 37 mg/m<sup>3</sup> monoglyme:

0.037 g/90.12 g/mol  $\approx$  0.00041 mol = 0.41 mmol  $\approx$  10 ppm.

0.031 g/76.09 g/mol  $\approx$  0.00041 mol = 0.41 mmol  $\approx$  10 ppm.

To evaluate the risk of monoglyme and its metabolite 2-ME, the lowest NO(A)ECs observed from developmental toxicity studies using 2-ME (9 mg/m<sup>3</sup>) and monoglyme (37 mg/m<sup>3</sup>) were considered. This approach is considered to be protective for susceptible subpopulations (pregnant women, fetuses and newborns) and to account for male reproductive system effects observed in different animal studies (LOAEC = 93 mg/m<sup>3</sup> for 2-ME; LOAEC = 935 mg/m<sup>3</sup> for monoglyme). Based on concentrations of monoglyme in indoor air, a comparison to the relevant NO(A)ECs results in MOEs of 823 to 2850. However, note that the rabbit inhalation developmental toxicity study showed fetal effects at 156 mg/m<sup>3</sup>, whereas the skeletal variations observed at 31 mg/m<sup>3</sup> of 2-ME are of unknown biological significance. The use of a NOEC (9 mg/m<sup>3</sup>) for this study is considered to be protective of susceptible populations, as stated above. The rat inhalation developmental toxicity study using monoglyme itself showed fetal skeletal and visceral effects at 120 mg/m<sup>3</sup>, and the resultant MOE for the indoor air scenario based on the NOAEC from this study was greater than 2800. Thus, there is a high level of confidence in the conservativeness of the MOEs developed.

Modelled product concentrations (see “Exposure Assessment” section) were lower than reported indoor air concentrations; therefore, the MOEs for these modelled scenarios

were not derived. Based on both the lowest NO(A)ECs for monoglyme and 2-ME, all derived MOEs are considered adequate to account for uncertainties in the health effects and exposure databases.

One of the metabolites of monoglyme, 2-ME, was previously assessed by Environment Canada and Health Canada (2002b) and was determined to be of high hazard potential due to a range of adverse effects in experimental animals, including the developmental toxicity described above. As a result, it is currently listed on Schedule 1 (Toxic Substances List) of CEPA 1999 (<http://www.ec.gc.ca/toxiques-toxics/Default.asp?lang=En&n=98E80CC6-0&xml=6874E3A4-D3CE-4E32-A644-FD75A7B9D059>). While exposure of the general population to monoglyme is not of concern at current levels, it might have a potential health effect of concern should exposures increase and should levels of its metabolite 2-ME increase.

## 7.4 Uncertainties in Evaluation of Risk to Human Health for the Ethylene Glycol Ethers

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

**Table 7-16. Sources of uncertainty in the risk characterization**

Key source of uncertainty	Impact
Lack of chronic studies for majority of the seven ethylene glycol ether substances.	-
Route-to-route extrapolation of oral dose toxicity studies for dermal exposures	+
Use of sub-chronic toxicity studies for long-term exposures	-
Significance of skeletal variations as an adverse developmental endpoint for monoglyme	+

+ = 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.

In the available health effects database, there were no chronic studies for most of the EGEs. Extrapolation from subchronic studies or from one exposure route to another exposure route due to lack of an appropriate dermal and/or inhalation study may also contribute some additional uncertainties. However, for the available dermal toxicity studies in the EGs and EGEs subgroups (TTEG, DEGEE, DEGBE, EGBEA), there was no evidence of health effects below the limit dose of 1000 mg/kg bw/day.

For monoglyme, developmental effects based on inhalation exposure to either monoglyme or 2-ME occurred at concentrations of 120 to 156 mg/m<sup>3</sup> in three different species. An increased incidence of skeletal variations was observed in only one of three species (rabbit) at lower concentrations. The biological significance of skeletal variations at these lower concentrations is uncertain.



Limited data were available on consumer use exposure patterns (duration of exposure) associated with air fresheners, window cleaners and tanning products. Also, uncertainties are associated with the market share and prevalence of high concentration EGE-containing cosmetic products in Canada. As stated in the “Exposure Assessment” section, although some of the EGEs may occur in several cosmetic products (e.g., DEGEE), aggregate exposures for individual substances were not estimated because they are not expected to account for a significant market share in Canada. Additionally, there may be uncertainty related to proportion of products used by consumers with the presence of monoglyme as an impurity.

## **8. Conclusion**

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from the seven substances in the Ethylene Glycol Ethers group. It is proposed to conclude that the seven substances in the Ethylene Glycol Ethers group do not meet the criteria under paragraphs 64(a) or (b) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Based on the information presented in this draft screening assessment, it is proposed to conclude that the seven substances in the Ethylene Glycol Ethers group do not meet the criteria under paragraph 64(c) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

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## Appendices

### Appendix A. Exposure Estimate Parameters for Ethylene Glycol Ethers from Use of Products

Exposures were estimated based on the assumed weight (70.9 kg) of an adult (Health Canada 1998), inhalation rate of an adult (16.2 m<sup>3</sup>/day) and use behaviours of an adult, unless noted otherwise. Exposures were estimated using ConsExpo version 4.1 or algorithms from the model (ConsExpo 2006).

**Table A-1. Exposure estimate parameters for Ethylene Glycol Ethers from use of products**

Product type and scenario	Substances	Model parameter
<b>Personal care products:</b>  Permanent hair dye (wash-in)	DEGEE; DEGBE	Concentration of DEGEE = 3-10% <sup>33</sup> DEGBE = 1–3% (personal communication, emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated September 2015; unreferenced) Product Amount = 100 g per application (RIVM 2006a) Frequency = 3.57 times per year (Statistics Canada 2012) Retention Factor = 0.10 (SCCS 2012)
<b>Personal care products:</b>  Tanning product	DEGEE	Concentration of DEGEE = 3–10% (personal communication, emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated September 2015; unreferenced) Product Amount = 4.4 g per day (application) (Loretz et al. 2005) Frequency = 1 application per day (expert judgement)

<sup>33</sup> 97.5% of hair dyes in Canada contain 3–10% DEGEE; only 2.5% contain >10%.

<b>Product type and scenario</b>	<b>Substances</b>	<b>Model parameter</b>
<b>Personal care products:</b>  Body cream	TEG; DEGEE	Concentration of TEG = $\leq 0.3\%$ ; DEGEE = 1–3% (personal communication, emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated September 2015; unreferenced) Product Amount = 4.4 g per application (Loretz et al. 2005) Frequency = 1.1 times per day (Loretz et al. 2005)
<b>Personal care products:</b>  Facial makeup	DEGBE	Concentration of DEGBE = 10–30% (personal communication, emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated September 2015; unreferenced) Product Amount = 1.2 g per application (Loretz et al. 2006) Frequency = 1.8 times per day (Loretz et al. 2006)
<b>Personal care products:</b>  Antibacterial shampoo	DEG	Concentration of DEG = 3% personal communication, emails from the Health Products and Food Branch, Health Canada, to the Risk Management Bureau, Health Canada, dated October 2015; unreferenced) Product Amount = 11.8 g per application (Loretz et al. 2006) Frequency = 1.1 times per day (Loretz et al. 2006)
<b>Personal care products:</b>  Deodorant/anti-perspirant	DEGEE	Concentration of DEGEE = 10–30% (personal communication, emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated September 2015; unreferenced) Product Amount = 0.6 g per application (Loretz et al. 2006) Frequency = 1.3 times per day (Loretz et al. 2006)
<b>Paints and coatings:</b>  Waterborne roller wall paint <sup>a</sup>	DEG	Concentration of DEG in paint colourant = 13% (MSDS 2012c) Pigment in wall paint = 8% (RIVM 2007a) Therefore, maximum expected concentration of DEG in whole paint = 1% Dermal absorption rate = 50% (DOW 2016a)
<b>Paints and</b>	TEG; TTEG	Industry data submitted under section 71 of CEPA 1999 indicated that TEG is present in concentrations between the

<b>Product type and scenario</b>	<b>Substances</b>	<b>Model parameter</b>
<b>coatings:</b>  Waterborne roller wall paint <sup>a</sup>		range of 0.1 to 4 %. No data was available for TTEG concentrations in paints. However, industry submissions indicated a potential presence in paints and coatings. Therefore, the concentration of TEG in paint was used as a surrogate for TTEG and exposure is expected to be similar.
<b>Paints and coatings:</b>  Waterborne roller wall paint <sup>a</sup>	DEGBE	Maximum concentration of DEGBE = 2% (MSDS 2015u) Dermal absorption rate = 50% (SCCP 2006a) Mass transfer rate = 353 m/s (Thibodeaux; calculated from RIVM 2005, p. 41) MW matrix = 20.5 m/s (calculated from RIVM 2005, p. 41)
<b>Paints and coatings:</b>  Floor/ concrete/ stone sealant/ finish <sup>b</sup>	DEGEE	Concentration of DEGEE = 1–10% (MSDS 2012d) Dermal absorption rate = 50% (SCCP 2006a) Mass transfer rate = 22 m/s (Thibodeaux; calculated from RIVM 2005, p. 41) MW matrix = 27.6 m/s (calculated from RIVM 2005, p. 41)
<b>Paints and coatings:</b>  Wood/deck stain <sup>b</sup>	EGBEA	Concentration of EGBEA = 1–5% (MSDS 2010d) Dermal absorption rate = 30% (EC 2006-2008a) Mass transfer rate = 22 m/s (Thibodeaux; calculated from RIVM 2005, p. 41) MW matrix = 27.6 m/s (calculated from RIVM 2005, p. 41)
<b>Cleaning products and air fresheners:</b>  Window cleaner <sup>c</sup>	DEGEE; EGBEA	Concentration of DEGEE = 8% (OECD 2007: p. 61) Concentration of EGBEA = 5% (MSDS 2015v) Exposure duration = 24 h (expert judgement) Dermal estimate = instant application and constant rate values added (expert judgement)
<b>Cleaning products and air fresh-</b>	DEG; DEGBE	Concentration of DEGBE = 10% (MSDS 2013f) Concentration of DEG = 4% (personal communication, emails from the Health Products and Food Branch, Health Canada, to the Risk Management Bureau, Health Canada, dated October 2015; unreferenced)

Product type and scenario	Substances	Model parameter
<b>Paints:</b>  Bathroom cleaner <sup>d</sup>		Exposure duration = 24 h (expert judgement) Dermal estimate = instant application and constant rate values summed (expert judgement)
<b>Cleaning products and air fresheners:</b>  Air freshener <sup>e</sup>	TEG; DEGEE; Monoglyme	Concentration of DEGEE = 10–30% (MSDS 2014d,e) Concentration of TEG = 5–10% (MSDS 2009b) Concentration of monoglyme (as impurity of other EGEs used in air fresheners) = 0.01% (Environment Canada 2009). Aerosol air freshener (non-aqueous): Discharge rate = 0.9 g/sec; Use frequency = 1/day; Spray duration = 6 sec (IFRA 2012) Chronic exposure duration (for air fresheners containing DEGEE, TEG, or monoglyme) = 24 h (expert judgement) Acute exposure duration (for air freshener containing monoglyme) = 6 h (based on single day exposures in 2-ME rabbit and monoglyme rat developmental toxicity studies) Room volume = 20 m <sup>3</sup> (IFRA 2012; RIVM 2006b) Ventilation rate = 0.6/h (RIVM 2006b)

<sup>a</sup>. Exposures were estimated using the ConsExpo scenario for 'Brush/roller painting, waterborne wall paint' (RIVM 2007a). All recommended default values from this scenario were used, except for parameters listed below.

<sup>b</sup>. General coating on a floor (RIVM 2007b) best fit the product scenarios for a floor/concrete/stone finish/sealant and wood/deck stain. All recommended default ConsExpo values from this scenario were used, except for parameters listed here.

<sup>c</sup>. Exposures were estimated using the ConsExpo scenario for 'Glass cleaners' (RIVM 2006a). All recommended default values from this scenario were used, except for parameters listed here.

<sup>d</sup>. Exposures were estimated using the ConsExpo scenario for 'Bathroom cleaners' (RIVM 2006a). All recommended default values from this scenario were used, except for parameters listed here.

<sup>e</sup>. ConsExpo does not currently have a scenario for air fresheners. However, based on IFRA (2012) and internal consultations, the parameters used in ConsExpo v4.1 are listed under "Model parameter."