Draft Screening Assessment

Esters Group

Environment and Climate Change Canada
Health Canada

March 2022

Synopsis

Pursuant to section 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment of 14 of 16 substances referred to collectively under the Chemicals Management Plan (CMP) as the Esters Group. These 14 substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other human health concerns. Two of the 16 substances were determined to be of low concern through other approaches, and the decisions for these substances are provided in a separate report.[1] Accordingly, this screening assessment addresses the 14 substances listed in the table below, which will hereinafter be referred to as the Esters Group. The Chemical Abstracts Service Registry Numbers (CAS RN[2]), their *Domestic Substances List* (DSL) names and their common names are listed in the table below.

Substances in the Esters Group

CAS RN	DSL name	Common name
79-20-9[a]	Acetic acid, methyl ester	Methyl acetate
102-76-1	1,2,3-Propanetriol, triacetate	Triacetin
106-70-7 [a]	Hexanoic acid, methyl ester	Methyl hexanoate
109-60-4	Acetic acid, propyl ester	Propyl acetate
110-19-0	Acetic acid, 2-methylpropyl ester	Isobutyl acetate
111-82-0	Dodecanoic acid, methyl ester	Methyl dodecanoate
577-11-7	Butanedioic acid, sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt	Docusate sodium
623-42-7[a]	Butanoic acid, methyl ester	Methyl butanoate
1119-40-0	Pentanedioic acid, dimethyl ester	Dimethyl glutarate
3234-85-3	Tetradecanoic acid, tetradecyl ester	Tetradecyl tetradecanoate

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[1] Conclusions for the substances bearing CAS RNs 111-55-7 and 122-79-2 are provided in the Substances Identified as Being of Low Concern using the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Screening Assessment.

[2] 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	DSL name	Common name
6846-50-0	Propanoic acid, 2-methyl-, 2,2-dimethyl-1-(1-methylethyl)-1,3-propanediyl ester	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate
25265-77-4	Propanoic acid, 2-methyl-, monoester with 2,2,4-trimethyl-1,3-pentanediol	Texanol
68990-53-4[b]	Glycerides, C14-22 mono-	C14-22 monoglycerides
70657-70-4[a]	1-Propanol, 2-methoxy-, acetate	2-Methoxypropyl acetate

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

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

According to information submitted in response to CEPA section 71 surveys, 12 of the 14 substances were reported to be manufactured or imported in Canada in 2009 or 2011. Methyl acetate, isobutyl acetate, dimethyl glutarate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate and docusate sodium were reported to be manufactured in Canada at volumes between 100 kg and 10 000 kg, whereas triacetin was reported to be manufactured between 10 000 kg and 100 000 kg. Reported import volumes of the substances in the Esters Group ranged from approximately 5 000 kg to more than 3 000 000 kg. Methyl hexanoate and methyl butanoate were not reported to be imported or manufactured above reporting threshold values in 2011.

Seven of the 14 substances in the Esters Group (methyl acetate, triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate and methyl butanoate) are naturally occurring in various fruits or plants. Several substances in the Esters Group are primarily used as solvents, including methyl acetate, propyl acetate, isobutyl acetate, methyl dodecanoate, dimethyl glutarate, triacetin, and 2,2,4-trimethyl-1,3-pentanediol diisobutyrate. Other primary uses include as plasticizers (triacetin, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate) or as skin conditioning agents (tetradecyl tetradecanoate). Most of the substances in the Esters Group are used in a range of industrial and commercial products and are also used in products available to consumers, including cosmetics, natural health products, prescription and/or non-prescription drugs, as well as in paints, adhesives, air fresheners, paint removers, fiberglass repair products, and concrete crack repair products. Methyl acetate, triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate and methyl butanoate may be used as food flavouring agents. Triacetin and docusate sodium are permitted food additives in Canada. C14-22 monoglycerides is included with the substances monoglycerides or mono- and di-glycerides, which are also permitted food additives in Canada.

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

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from the substances in the Esters Group. It is proposed to conclude that methyl acetate, triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, docusate sodium, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, C14-22 monoglycerides, and 2-methoxypropyl acetate 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.

With respect to human health, 8 of the 14 substances in the Esters Group were considered to be of low hazard potential, namely triacetin, propyl acetate, isobutyl acetate, methyl dodecanoate, dimethyl glutarate, tetradecyl tetradecanoate, texanol, and C14-22 monoglycerides. Risk to human health for these substances is therefore considered to be low.

Developmental toxicity is a potential critical effect of methyl acetate due to the rapid hydrolysis of the substance to methanol. Potential developmental effects of methanol were reviewed in the draft screening assessment for the Alcohols Group under the CMP and were taken into consideration in the characterization of risk to human health from exposure to methyl acetate. The predominant routes of exposure to methyl acetate for the general population are expected to be through natural occurrence in food and indoor air and through the use of various products containing the substance including nail products, cleaning products, automotive products (e.g., aerosol paints, tire cleaners), adhesives (e.g., construction adhesives, aerosol adhesives for fabric and tube glues), adhesive removers, lubricants, paint strippers or removers (referred to as paint removers in this document), and floor coatings. On the basis of comparisons of the levels of exposure to methyl acetate from environmental media and food as well as through the use of products available to consumers outlined above (excluding paint removers and aerosol adhesives) with established reference levels for methanol that were adjusted for exposure to methyl acetate, potential risk to human health is expected to be low. Methanol reference levels of exposure were used because methanol is a hydrolysis product of methyl acetate and because no reference levels currently exist for methyl acetate. Use of paint remover products and aerosol adhesives containing methyl acetate resulted in estimates of exposure to methyl acetate that were higher than established reference concentrations for methanol (when adjusted for exposure to methyl acetate), suggesting a potential risk to human health.

Following absorption, methyl hexanoate and methyl butanoate are expected to undergo hydrolysis to form their respective carboxylic acids (i.e., hexanoic acid and *n*-butyric acid, respectively) and methanol.

Developmental toxicity is a potential critical effect of methyl hexanoate and methyl butanoate due to the hydrolysis of these substances to form methanol.

Exposure of the general population to methyl hexanoate and methyl butanoate may occur via indoor air or use as a food flavouring agent. Methyl hexanoate is also found in nail products. On the basis of comparisons of the levels of exposure to methyl hexanoate and methyl butanoate with established reference levels for methanol (with methanol reference values adjusted for exposure to methyl hexanoate and methyl butanoate, respectively), the potential risk to human health is expected to be low. Methanol reference levels were used because methanol is a hydrolysis product of both methyl hexanoate and methyl butanoate and because no reference levels currently exist for the aforementioned substances.

The critical effect of 2-methoxypropyl acetate is considered to be developmental toxicity. Potential sources of exposure to 2-methoxypropyl acetate for the general population are expected to be air and water, and the use of products such as cosmetics, aerosol paints or putty fillers. The margins of exposure between estimated exposure to 2-methoxypropyl acetate and critical effect levels are considered adequate to address uncertainties in the health effects and exposure datasets.

The available health effects information on 2,2,4-trimethyl-1,3-pentanediol diisobutyrate indicates potential effects on the reproductive system. Sources of exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate for the general population are expected to occur predominantly via indoor air and the use of various products containing the substance, including nail products, cosmetic adhesives, natural health products, aerosol primer, pool paint, hobby paints, fiberglass repair products, and concrete crack repair products. Oral exposure of children to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate may also result from its migration from baby bottles made from materials used as substitutes for polycarbonate and plastic toys. The margins of exposure between critical effects and estimates of exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate are considered adequate to account for uncertainties in the health effects and exposure datasets.

Docusate sodium was reviewed in the United States Environmental Protection Agency (US EPA) screening-level hazard characterization of the sulfosuccinates category in 2009, and that review informs the health effects characterization in this assessment. Critical effects following subchronic oral exposures to docusate sodium were site-of-contact effects on the gastrointestinal tract and decrease in body weight gain observed in rats. Repeated oral exposure to docusate sodium in rats was also associated with developmental effects, but only in the presence of maternal toxicity. Sources of exposure to docusate sodium for the general population are expected to be through its use as a permitted food additive and from the use of products containing the substance, including cosmetics, natural health products, prescription and/or non-prescription drugs, cleaning products, wallpaper paste activator and hardener products. The margins of exposure between estimated exposure to docusate sodium and critical effects level are considered adequate to address uncertainties in the health effects and exposure datasets.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that methyl acetate meets the criteria under paragraph 64(*c*) of CEPA as it is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, docusate sodium, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, C14-22 monoglycerides, and 2-methoxypropyl acetate do not meet the criteria under paragraph 64(*c*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore proposed to conclude that methyl acetate meets one or more of the criteria set out in section 64 of CEPA.

It is also proposed to conclude that triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, docusate sodium, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, C14-22 monoglycerides, and 2-methoxypropyl acetate do not meet any of the criteria set out in section 64 of CEPA.

It is also proposed that methyl acetate meets the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

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1. Introduction

Pursuant to section 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have conducted a screening assessment of 14 of 16 substances, referred to collectively under the Chemicals Management Plan (CMP) as the Esters Group, to determine whether these 14 substances present or may present a risk to the environment or to human health. These 14 substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other human health concerns (ECCC, HC [modified 2017]).

The other 2 substances (CAS RN[3] 111-55-7, 1,2-ethanediol, diacetate; CAS RN 122-79-2, acetic acid, phenyl ester) were considered in the Ecological Risk Classification of Organic Substances (ERC) and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Science Approach Documents (ECCC 2016a; Health Canada 2016), and were identified as being of low concern to both human health and the environment. As such, they are not further addressed in this report. Conclusions for these 2 substances are provided in the Substances Identified as Being of Low Concern Using the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Screening Assessment (ECCC, HC 2018). The 14 substances addressed in this screening assessment will hereinafter be referred to as the Esters Group.

The ecological risks of substances in the Esters Group were characterized using the ERC approach (ECCC 2016a). The ERC describes the hazard of a substance using key metrics including mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity, and considers the possible exposure of organisms in the aquatic and terrestrial environments on the basis of 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.

Some substances in the Esters Group have been reviewed internationally by the European Union (EU), the United States Environmental Protection Agency (US EPA), and through the Organisation for Economic Co-operation and Development (OECD) Cooperative Chemicals Assessment Programme. Health Canada considers these

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assessments to be reliable, and they were used to inform the health effects characterization in this screening assessment.

This draft screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposures, including additional information submitted by stakeholders. Relevant data were identified up to March 2021. 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 Program at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The human health portion of this assessment has undergone external peer review and/or consultation. Comments on the technical portions relevant to human health were received from Dr. Warren Foster (McMaster University), Dr. David Dorman (North Carolina State University) and Dr. Calvin Willhite (Risk Sciences International). External peer review comments provided on the methanol section of the Alcohols Group draft screening assessment were also relevant to this assessment. The ecological portion of this assessment is based on the ERC document (published July 30, 2016), which was subject to an external review as well as a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

This draft screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by examining scientific information and incorporating a weight of evidence approach and precaution.[4] This draft screening assessment presents the critical information and considerations on which the proposed conclusions are based.

2. Identity of substances

The CAS RN, *Domestic Substances List* (DSL) names and common names for the individual substances and/or representative substances in the Esters Group are

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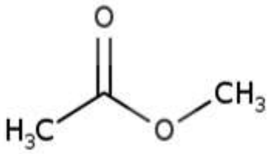
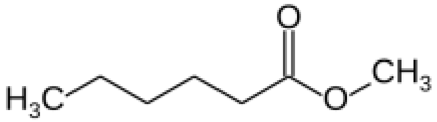
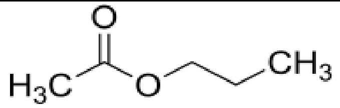
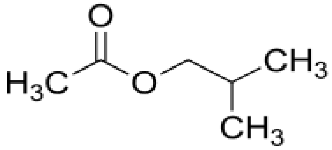
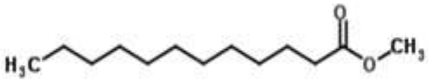
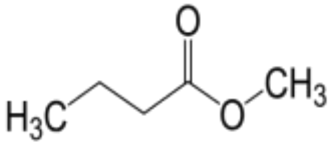
[4] A determination of whether one or more of the criteria of section 64 of CEPA are met is based on an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient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

presented in Table 2-1 to Table 2-1. Although each ester is assessed individually, for presentation of the information in this screening assessment, they have been organized into four subgroups based on similarities in chemical structure. Subgroup A consists of esters of acyclic linear or branched alcohols with linear carboxylic acid(s); subgroup B contains esters of di/tri-ols; subgroup C contains esters of 2,2,4-trimethylpentane-1,3-diol with isobutyric acid; and subgroup D contains one individual substance which is a salt of a diester.

Table 2-1. Substance identities (subgroup A): Esters of acyclic linear or branched alcohols with linear carboxylic acid(s)

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
79-20-9	Acetic acid, methyl ester (methyl acetate)	 $C_3H_6O_2$	74.08
106-70-7	Hexanoic acid, methyl ester (methyl hexanoate)	 $C_7H_{14}O_2$	130.19
109-60-4	Acetic acid, propyl ester (propyl acetate)	 $C_5H_{10}O_2$	102.13
110-19-0	Acetic acid, 2-methylpropyl ester (isobutyl acetate)	 $C_6H_{12}O_2$	116.16
111-82-0	Dodecanoic acid, methyl ester (methyl dodecanoate)	 $C_{13}H_{26}O_2$	214.35
623-42-7	Butanoic acid, methyl ester (methyl butanoate)	 $C_5H_{10}O_2$	102.13

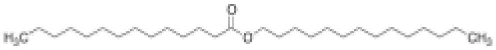
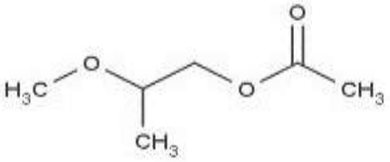
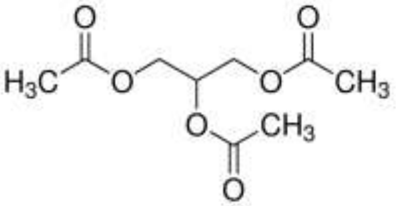
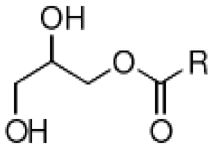
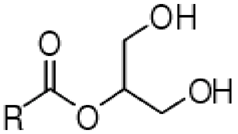
CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
1119-40-0	Pentanedioic acid, dimethyl ester (dimethyl glutarate)	 $C_7H_{12}O_4$	160.17
3234-85-3	Tetradecanoic acid, tetradecyl ester (tetradecyl tetradecanoate)	 $C_{28}H_{56}O_2$	424.75
70657-70-4	1-Propanol, 2-methoxy-, acetate (2-methoxypropyl acetate)	 $C_6H_{12}O_3$	132.16

Table 2-2. Substance identities (subgroup B): Esters of di/tri-ols

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
102-76-1	1,2,3-Propanetriol, triacetate (triacetin)	 $C_9H_{14}O_6$	218.20

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
68990-53-4 [a]	Glycerides, C14-22 mono-	Representative structures: 1-monoacylglycerol:  2-monoacylglycerol: 	N/A

Abbreviation: N/A, Not applicable

[a] This CAS RN is a UVCB (unknown or variable composition, complex reaction products, or biological materials). These materials are derived from natural sources or complex reactions and cannot practicably be synthesized by simply combining individual constituents. A UVCB is not an intentional mixture of discrete substances and is considered a single substance.

Table 2-3. Substance identities (subgroup C): Esters of 2,2,4-trimethylpentane-1,3-diol with isobutyric acid

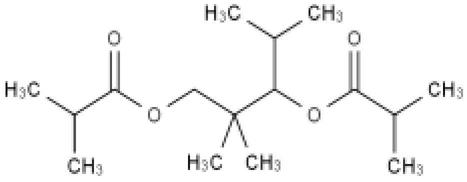
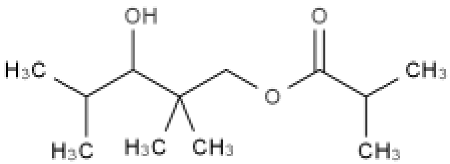
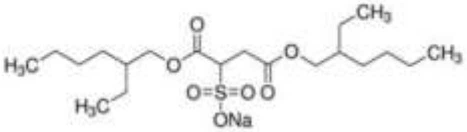
CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
6846-50-0	Propanoic acid, 2-methyl-, 2,2-dimethyl-1-(1-methylethyl)-1,3-propanediyl ester (2,2,4-trimethyl-1,3-pentanediol diisobutyrate)	 $C_{16}H_{30}O_4$	286.41
25265-77-4	Propanoic acid, 2-methyl-, monoester with 2,2,4-trimethyl-1,3-pentanediol (texanol)	 $C_{12}H_{24}O_3$	216.32

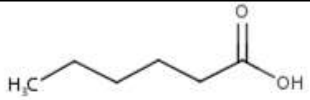
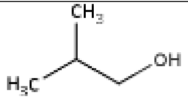
Table 2-4. Substance identities (subgroup D): Salt of a diester

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
577-11-7	Butanedioic acid, sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt (docusate sodium)	 $C_{20}H_{37}NaO_7S$	444.57

2.1 Use of metabolite and analogue data

Data from metabolites as well as analogues have been used to inform the human health assessment of certain substances in subgroup A. After absorption, esters undergo rapid hydrolysis by non-specific esterases present in the body. Data on the expected metabolites (acid and alcohols) were used to inform the human health assessment of certain substances in subgroup A. Analogues that were structurally and/or functionally similar to substances within this group (similar physical-chemical properties, toxicokinetics) were selected and used for read-across. A list of the various metabolites and analogues used to inform the Esters Group assessment is presented in Table 2-5 and Table 2-6, respectively. For further information on the physical-chemical properties of analogues, please refer to Appendix A. Details of the selection of analogues are further discussed in the relevant sections of this report.

Table 2-5. Metabolite identities

CAS RN	Common name	Chemical structure and molecular formula	Molecular weight (g/mol)	Used to inform assessment of:
67-56-1	Methanol	 CH_3OH	32.04	Methyl acetate ; Methyl hexanoate; Methyl butanoate
142-62-1	Hexanoic acid	 $C_6H_{12}O_2$	116.16	Methyl hexanoate
71-23-8	*n*-Propyl alcohol	 C_3H_8O	60.10	Propyl acetate
78-83-1	Isobutanol	 $C_4H_{10}O$	74.12	Isobutyl acetate

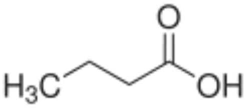
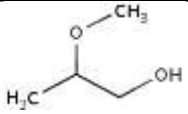
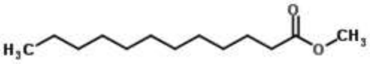
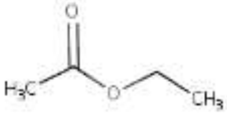
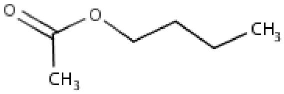
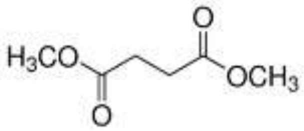
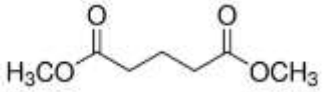
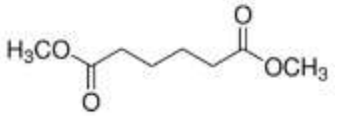
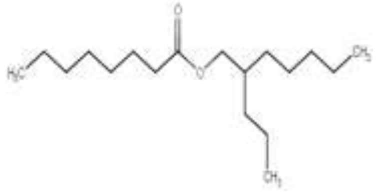
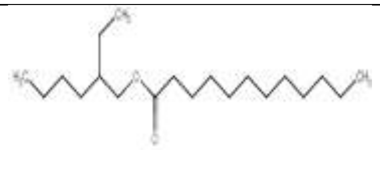
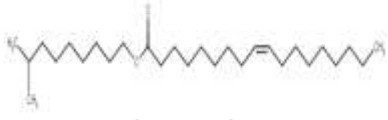
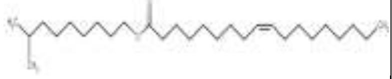
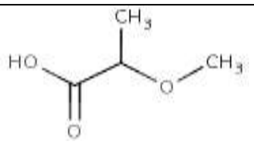
CAS RN	Common name	Chemical structure and molecular formula	Molecular weight (g/mol)	Used to inform assessment of:
107-92-6	*n*-Butyric acid	 $C_4H_8O_2$	88.11	Methyl butanoate
544-63-8	Myristic acid	 $C_{14}H_{28}O_2$	228.37	Tetradecyl tetradecanoate
75782-87-5	Alcohols, C14-15	 $C_{14}H_{30}O$	214.39	Tetradecyl tetradecanoate
112-72-1	Tetra-decanol	 $C_{14}H_{30}O$	214.39	Tetradecyl tetradecanoate
1589-47-5	2-Methoxy-propanol	 $C_4H_{10}O_2$	90.12	2-Methoxypropyl acetate

Table 2-6. Analogue identities

CAS RN	Common name (acronym)	Chemical structure and molecular formula	Molecular weight (g/mol)	Used to inform assessment of:
111-82-0	Methyl dodecanoate	 $C_{13}H_{26}O_2$	214.35	Methyl hexanoate; Methyl butanoate
141-78-6	Ethyl acetate	 $C_4H_8O_2$	88.11	Propyl acetate
123-86-4	*n*-Butyl acetate	 $C_6H_{12}O_2$	116.16	Propyl acetate

CAS RN	Common name (acronym)	Chemical structure and molecular formula	Molecular weight (g/mol)	Used to inform assessment of:
95481-62-2	Dibasic esters (DBE)	Mixture: Dimethyl succinate (CAS RN 106-65-0)  $C_8H_{14}O_4$ Dimethyl glutarate (CAS RN 1119-40-0  $C_7H_{12}O_4$ Dimethyl adipate (CAS RN 627-93-0)  $C_6H_{10}O_4$	N/A	Dimethyl glutarate
868839-23-0	Propylheptyl caprylate	 $C_{18}H_{36}O_2$	284.48	Tetradecyl tetradecanoate
20292-08-4	Ethylhexyl laurate	 $C_{20}H_{40}O_2$	312.53	Tetradecyl tetradecanoate
94247-10-6	Isodecyl laurate	 $C_{22}H_{44}O_2$	340.59	Tetradecyl Tetradecanoate

CAS RN	Common name (acronym)	Chemical structure and molecular formula	Molecular weight (g/mol)	Used to inform assessment of:
110-27-0	Isopropyl myristate	 $C_{17}H_{34}O_2$	270.45	Tetradecyl tetradecanoate
59231-34-4	Isodecyl oleate	 $C_{28}H_{54}O_2$	422.73	tetradecyl tetradecanoate
22393-85-7	Tetradecyl oleate	 $C_{32}H_{62}O_2$	478.84	Tetradecyl tetradecanoate
17671-27-1	Behenyl behenate	 $C_{44}H_{88}O_2$	649.18	Tetradecyl tetradecanoate
22047-49-0	2-Ethylhexyl stearate	 $C_{26}H_{52}O_2$	396.69	Tetradecyl tetradecanoate
4324-37-2	2-Methoxy-propanoic acid	 $C_4H_8O_3$	104.10	2-Methoxypropyl acetate

Abbreviation: N/A, Not applicable

3. Physical and chemical properties

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

Table 3-1. Experimental physical and chemical property values (at a standard temperature of 25°C) for substances in the Esters Group (subgroup A)

Property	Methyl acetate	Methyl hexanoate	Propyl acetate	Isobutyl acetate	Methyl dodecanoate
Physical state	liquid	liquid	liquid	liquid	liquid
Melting point (°C)	-98.0	-71	-93	-98.8	5.2
Vapour pressure (Pa)	28 800	496	4786	2373	0.55

Property	Methyl acetate	Methyl hexanoate	Propyl acetate	Isobutyl acetate	Methyl dodecanoate
Henry's law constant (atm·m^3/mol)	1.15×10^{-4}	3.67×10^{-4}	2.18×10^{-4}	4.54×10^{-4}	2.98×10^{-3a}
Water solubility (mg/L)	243 000 (at 20°C)	1 330 (at 20°C)	18 900 (at 20°C)	6 300	0.9-1.4[a]
log K_{ow} (dimensionless)	0.18	2.34[a]	1.24	1.78	5.41
log K_{oc} (dimensionless)	0.49-0.96[a]	1.55-2.1[a]	1.0-1.5[a]	1.2-1.8[a]	3.1-3.9[a]
pK_a (dimensionless)	-7[b]	-7[b]	-7[b]	-7[b]	-7[b]

Abbreviations: K_{ow}, octanol–water partition coefficient; log K_{oc} soil adsorption coefficient; pK_a, negative log function of the acid dissociation constant

All references from ChemIDplus (1993-) except when noted otherwise

[a] Estimated from EPI Suite (c2000-2012)

[b] Wishart et al. (2013) (estimated values found in (Human Metabolome Database (HMDB))

Table 3-2. Experimental physical and chemical property values (at a standard temperature of 25°C) for substances in the Esters Group (subgroup A, continued)

Property	Methyl butanoate	Dimethyl glutarate	Tetradecyl tetradecanoate	2-Methyoxypropyl acetate
Physical state	liquid	liquid	solid	liquid
Melting point (°C)	-85.8	-42.5	162.8[a]	-50.3[a]
Vapour pressure (Pa)	4 306	24	2.1×10^{-6a}	1029[a]
Henry's law constant (atm·m^3/mol)	2.05×10^{-4}	6.43×10^{-7}	2.1×10^{-1} -6.3×10^{-1a}	3.62×10^{-6} – 5.9×10^{-7a}
Water solubility (mg/L)	15 000	59 000	3.4×10^{-8a}	32 660[a]
log K_{ow} (dimensionless)	1.29	0.62	12.7[a]	0.52[a]
log K_{oc} (dimensionless)	1.0-1.6[a]	1.0-1.1[a]	7.0-7.9[a]	0.60-1.1[a]
pK_a (dimensionless)	-7[b]	N/A	N/A	N/A

Abbreviations: K_{ow}, octanol–water partition coefficient; log K_{oc} soil adsorption coefficient; pK_a, negative log function of the acid dissociation constant; N/A, not available
All references from ChemIDplus (1993-) except when noted otherwise.
[a] Modelled using EPI Suite (c2000-2012)
[b] Wishart et al. (2013) (estimated values found in HMDB database)

Table 3-3. Experimental physical and chemical property values (at a standard temperature of 25°C) for substances in the Esters Group (subgroups B, C and D)

Property	**Triacetin**	**Glycerides, C14-22 mono-**	**2,2,4-Trimethyl-1,3-pentanediol diisobutyrate**	**Texanol**	**Docusate sodium**
Physical state	liquid	solid[a]	liquid	liquid	solid
Melting point (°C)	-78.0	139[b]	-70[c]	-50[c] ;-70[d]	176
Vapour pressure (Pa)	0.33	6.4 × 10^{-7}[b]	1.13[b]	1.3[c] (at 20°C)	1.63 × 10^{-12}[b]
Henry's law constant (atm·m^3/mol)	1.23 × 10^{-8}[b]	1.2 × 10^{-8} – 3.1 × 10^{-12}[b]	1.1 × 10^{-5} [b]	1.1 × 10^{-7} - 8.21 × 10^{-8}[b]	5.00 × 10^{-12}[b]
Water solubility (mg/L)	58 000	Insoluble in water[a]	0.94[b]- 13[d]	322[b]	71 000
log K_{ow} (dimensionless)	0.25	4.65[b]	4.91[b]	3.0[b]	2.0[g] - 3.95[b]
log K_{oc} (dimensionless)	0.9-1.6[b]	1.9-2.6[b]	2.7-3.5[b]	1.5 – 2.1[b]	2.80[b]
pK_a (dimensionless)	-6.5[e]	N/A	N/A	16.97[f]	N/A

Abbreviations: K_{ow}, octanol–water partition coefficient; log K_{oc} soil adsorption coefficient; pK_a, negative log function of the acid dissociation constant; N/A, not available
All references from ChemIDplus (1993-) except when noted otherwise.
[a] Norn (2015)
[b] Modelled using EPI Suite (c2000-2012)
[c] PubChem (NCBI 2004-)
[d] ECHA (c2007-2017a)
[e] Wishart et al. (2013) (HMDB database of estimated values)
[f] ECHA (c2007-2017b) (estimated value)
[g] ECHA (c2007-2017c)

4. Sources and uses

All of the substances in the Esters Group have been included in surveys issued pursuant to section 71 of CEPA (Canada 2009, 2012). Table 4-1 presents a summary of information reported on the total manufacture and import quantities for the Esters Group. According to information submitted in response to a CEPA section 71 survey, methyl hexanoate and methyl butanoate were not reported to be manufactured in or imported into Canada above the reporting threshold in 2011 (Environment Canada 2013). For the remaining 12 esters, manufacturing quantities ranged from 0 kg to 100 000 kg and import quantities ranged from 5 000 kg to more than 3 000 000 kg in

2011 (for 11 substances) or 2009 (for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate) (Environment Canada 2009, 2013).

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

Common name (CAS RN)	Total manufacture[a] (kg)	Total imports[a] (kg)	Reporting year
Methyl acetate (79-20-9)	9 600	323 602	2011
Methyl hexanoate (106-70-7)	NR	NR	2011
Propyl acetate (109-60-4)	NR	3 341 393	2011
Isobutyl acetate (110-19-0)	710	100 000 – 1 000 000	2011
Methyl dodecanoate (111-82-0)	NR	10 000 – 100 000	2011
Methyl butanoate (623-42-7)	NR	NR	2011
Dimethyl glutarate (1119-40-0)	1 000 – 10 000	122 144	2011
Tetradecyl tetradecanoate (3234-85-3)	NR	31 626	2011
2-Methoxypropyl acetate (70657-70-4)	NR	5 752	2011
Triacetin (102-76-1)	10 000 – 100 000	100 000 – 1 000 000	2011
Glycerides, C14-22 mono- (68990-53-4)	NR	43 000	2011
2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (6846-50-0)	100 – 10 000	594 600	2009
Texanol (25265-77-4)	NR	2 541 030	2011
Docusate sodium (577-11-7)	100 – 1 000	1 081 185	2011

Abbreviation: NR, not reported above the reporting volume of 100 kg.

[a] Values reflect quantities reported in response to the surveys conducted under section 71 of CEPA (Canada 2009, 2012). See surveys for specific inclusions and exclusions (schedules 2 and 3).

Subgroup A

Methyl acetate is primarily used as a solvent in a variety of commercial products and in products available to consumers in Canada, including paints and coatings, paint strippers or removers (referred to as paint removers in this document), adhesives and sealants, cleaning products, and furnishing care products (Environment Canada 2013; SDS 2018a). Propyl acetate has reported uses as a solvent, pigment and paint additive in a range of commercial products and products available to consumers, including paints and coatings, inks, toners and colourants and personal care products (Environment Canada 2013). Isobutyl acetate is used as a solvent in paints and coatings (Environment Canada 2013). Methyl dodecanoate functions as a solvent for cleaning or degreasing (Environment Canada 2013). Functions of dimethyl glutarate include use as a processing aid, adhesive, sealant and solvent in commercial products and in products available to consumers, including paints and coatings, personal care products (cosmetics), adhesives and sealants, and building or construction materials, as well as in oil and natural gas extraction and automotive, aircraft and transportation applications (Environment Canada 2013). Tetradecyl tetradecanoate is primarily used as a skin conditioning agent in personal care products and cosmetics in Canada (Environment Canada 2013). The primary applications of 2-methoxypropyl acetate include its use in paints and coatings, as well as in plastic and rubber material, where it functions as a finishing agent (Environment Canada 2013).

Methyl acetate, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, and methyl butanoate have been reported to occur naturally in food and may be used internationally as food flavouring agents in a variety of foods (Burdock 2010). No definitive information is available concerning the potential uses of these substances as food flavouring agents in Canada. However, since these substances are identified as food flavouring agents internationally, it is possible that they are present as flavouring agents in foods sold in Canada (personal communication, email from Food Directorate (FD), Health Canada (HC) to Existing Substances Risk Assessment Bureau (ESRAB), HC, dated December 5, 2016, and March 15, 2021; unreferenced).

Methyl acetate, propyl acetate, isobutyl acetate and 2-methoxypropyl acetate may be used as components in the manufacture of food packaging materials with no direct food contact. Dimethyl glutarate and tetradecyl tetradecanoate have been identified as components in incidental additives[5] (e.g., hand cleaners and hand sanitizers) used in processing establishments with no direct food contact (personal communication, emails

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[5] While not defined under the *Food and Drugs Act* (FDA), incidental additives may be regarded, for administrative purposes, as those substances that are used in food processing plants and that may potentially become adventitious residues in food (e.g., cleaners, sanitizers).

from FD, HC, to ESRAB, HC, dated December 5, 2016, and March 15, 2021; unreferenced).

Dimethyl glutarate is a medicinal ingredient in two registered disinfectant products; tetradecyl tetradecanoate is a non-medicinal ingredient in several over-the-counter topically applied therapeutic products, including gels, creams and lotions as well as lip moisturizers (personal communication, email from Therapeutic Products Directorate (TPD), HC, to ESRAB, HC, dated December 6, 2016; unreferenced).

Methyl acetate, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, and methyl butanoate are listed in the Natural Health Products Ingredients Database (NHPID) with a non-medicinal role for use as flavour enhancer. Dimethyl glutarate is listed in the NHPID with a non-medicinal role for use as solvent. Tetradecyl tetradecanoate is listed in the NHPID with a non-medicinal role for topical use only, up to 17%, when formulated to be non-irritating, as a skin-conditioning agent – emollient or skin-conditioning agent - occlusive (NHPID [modified 2021]). Tetradecyl tetradecanoate is listed in the Licensed Natural Health Products Database (LNHPD) as being present as a non-medicinal ingredient in natural health products in Canada, whereas methyl acetate, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, methyl butanoate and dimethyl glutarate are not listed (LNHPD [modified 2021]).

According to notifications submitted under the *Cosmetic Regulations* to Health Canada, methyl acetate, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, dimethyl glutarate, and tetradecyl tetradecanoate are used in certain cosmetics in Canada. Methyl acetate is used in products such as nail polishes, nail polish removers, cleansers, bath products, makeup, exfoliants and moisturizers. Methyl hexanoate was notified to be used in moisturizing products for nails. Propyl acetate was notified to be used in products such as nail polishes, makeup, and styling products. Isobutyl acetate was notified to be used in nail products and moisturizers. Methyl dodecanoate was found in face moisturizers. Dimethyl glutarate was notified to be used in products such as cleansers, adhesive removers and nail polish removers. Tetradecyl tetradecanoate was notified to be used in products such as antiperspirants, bath products, bleach, cleansers, conditioners, exfoliants, fragrance products, hair colours, makeup, massage products, moisturizers, nail polishes, shampoos, shaving products, styling products and sunless tanning products (personal communication, email from the Consumer and Hazardous Products Safety Directorate [CHPSD], HC, to ESRAB, HC, dated March 5, 2021; unreferenced).

2-Methoxypropyl acetate is described on the List of Prohibited and Restricted Cosmetic Ingredients (more commonly referred to as the Cosmetic Ingredient Hotlist or simply the Hotlist) as a prohibited substance. This list is an administrative tool that Health Canada uses to communicate that certain substances may contravene the general prohibition found in section 16 of the *Food and Drugs Act* (FDA), or may contravene one or more provisions of the *Cosmetic Regulations.* Section 16 of the FDA states that “No person shall sell any cosmetic that has in or on it any substance that may cause injury to the health of the user.” In addition, the Hotlist includes certain substances that may make it unlikely for a product to be classified as a cosmetic under the FDA (Health Canada 2015).

Methyl butanoate is not reported to be used in cosmetics in Canada (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced).

The following substances in subgroup A have been identified as formulants in pest control products registered in Canada: methyl acetate, propyl acetate, isobutyl acetate, methyl dodecanoate, and 2-methoxypropyl acetate.

Methyl acetate and isobutyl acetate have been identified as possible ingredients in vaping products (US FDA 2019), which may represent an additional source of exposure to methyl acetate and isobutyl acetate. Vaping products (such as electronic cigarettes and vaping devices containing cannabis) are being addressed through separate legislative frameworks (HC [modified 2020]).

Table 4-2 and Table 4-3 present a summary of the major uses of the esters in subgroup A according to information submitted in response to a CEPA section 71 survey (Environment Canada 2013). Additional uses of the esters in subgroup A are also identified in Table 4-5.

Table 4-2. Summary of Canadian uses of substances in the Esters Group (subgroup A) submitted in response to a CEPA section 71 survey

Major uses[a]	Methyl acetate	Propyl acetate	Isobutyl acetate	Methyl dodecanoate	Dimethyl glutarate
Adhesive and sealants	Y	N	Y	N	Y
Automotive aircraft and transportation	N	Y	Y	N	Y
Batteries	Y	N	N	N	N
Building or construction materials	N	N	N	N	Y
Cleaning and furnishing care	Y	N	N	N	N
Fabric, textile and leather articles	Y	N	N	N	N
Ink, toner and colourants	Y	Y	N	N	Y
Natural health products	Y	N	N	N	N
Oil and natural gas extraction	N	N	N	N	Y
Paints and coatings	Y	Y	Y	N	Y
Paper products, mixtures or manufactured items	Y	N	N	N	N
Personal care and cosmetics	N	Y	N	N	Y
Plastic and rubber materials not otherwise covered	Y	Y	N	N	N
Toys, playground and sporting equipment	N	N	N	N	Y
Water treatment	N	N	N	N	N
Other[b]	Y	Y	Y	Y	Y

Abbreviations: Y, yes; N, no

[a] Non-confidential uses reported in response to a CEPA section 71 survey (Environment Canada 2013). See survey for specific inclusions and exclusions (schedules 2 and 3).

[b] Other refers to minor uses and/or uses that cannot be disclosed as a result of confidentiality claims.

Table 4-3. Summary of Canadian uses of substances in the Esters Group (subgroup A, continued) submitted in response to a CEPA section 71 survey

Major uses[a]	Tetradecyl tetradecanoate	2-Methoxypropyl acetate
Automotive aircraft and transportation	N	Y
Drugs	Y	N
Natural health products	Y	N
Personal care and cosmetics	Y	N
Plastic and rubber materials not otherwise covered	N	Y

Abbreviations: Y, yes; N, no

[a] Non-confidential uses reported in response to a CEPA section 71 survey (Environment Canada 2013). See survey for specific inclusions and exclusions (schedules 2 and 3).

Subgroup B

According to information submitted in response to a CEPA section 71 survey, reported applications of triacetin include its use in personal care and cosmetic products, inks, toners and colourants, adhesives and sealants, and in food and beverages in Canada (Environment Canada 2013).

Triacetin has been identified as a component in an incidental additive (lubricant) used in food processing establishments with no direct food contact (personal communication, email from the FD, HC, to ESRAB, HC, dated December 5, 2016; unreferenced). Glycerides, C14-22 mono- has been identified in food packaging materials as a component in polystyrene-based materials (e.g., foam cups, containers) and polypropylene-based materials (e.g., containers, pails) and has been identified in incidental additives (e.g., lubricants and release agents) (personal communication, email from the FD, HC, to ESRAB, HC, dated November 23, 2015; unreferenced).

Both triacetin and glycerides, C14-22 mono- are considered to be permitted food additives in Canada. Triacetin is permitted for use as a wetting agent in cake mixes and as a solvent in flavours as prescribed in the *List of Permitted Food Additives with Other Accepted Uses* and the *List of Permitted Carrier or Extraction Solvents,* respectively, incorporated by reference into their respective Marketing Authorization issued under the *Food and Drugs Act.* Glycerides, C14-22 mono-, would be included under the permitted food additives uses for monoglycerides and mono- and di-glycerides, which are permitted for use as an emulsifying, gelling, stabilizing or thickening agent, as an antifoaming, humectant or release agent and as a carrier or extraction solvent in a variety of foods, as prescribed in the *List of Permitted Emulsifying, Gelling, Stabilizing or Thickening Agents*, the *List of Permitted Food Additives with Other Accepted Uses* and the *List of Permitted Carrier or Extraction Solvents*, incorporated by reference into their respective Marketing Authorization issued under the *Food and Drugs Act*.

Triacetin is listed in the NHPID with a non-medicinal role for use as a cosmetic biocide, flavour enhancer, fragrance ingredient, humectant, plasticizer or solvent, as well as in the LNHPD as being present as a non-medicinal ingredient in natural health products in Canada (NHPID [modified 2021]; LNHPD [modified 2021]). Triacetin is also used as a non-medicinal ingredient in approximately 25 prescription and/or non-prescription drugs registered in Canada. Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, triacetin is used in certain cosmetics in Canada such as adhesives, cleansers, exfoliants, makeup, makeup removers, massage products, moisturizers and nail polishes (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Triacetin is also a formulant in registered pest control products in Canada.

Subgroup C

According to information submitted in response to a CEPA section 71 survey, major uses of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in Canada include its use as a solvent in plastic and rubber materials, as well as in inks, toners and colourants, and in adhesives and sealants (Environment Canada 2009). It is also used as a curing agent and polymerization initiator, as well as in paints and coatings, floor coverings and formed automotive parts. In a separate survey, texanol was reported to be used in paints and coatings, adhesives and sealants, building or construction materials, automotive, aircraft and transportation applications, floor coverings, and fuels and related products (Environment Canada 2013).

Both 2,2,4-trimethyl-1,3-pentanediol diisobutyrate and texanol may be used as a component in the manufacture of food packaging materials with no direct food contact (personal communication, emails from FD, HC, to ESRAB, HC, dated December 5, 2016, and March 15, 2021; unreferenced).

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is listed in the NHPID with a non-medicinal role for topical use only, up to 9.8%, as plasticizer, as well as in the LNHPD as being present as a non-medicinal ingredient in a natural health product in Canada (NHPID [modified 2021]; LNHPD [modified 2018]).

According to notifications submitted under the *Cosmetic Regulations* to Health Canada, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate is used in certain cosmetics in Canada such as adhesives, nail moisturizers, nail polishes and nail polish removers. Texanol (identified by International Nomenclature of Cosmetic Ingredients [INCI] name of trimethyl pentanyl diisobutyrate) is used in nail polishes and make-up in Canada (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Texanol is also a formulant in registered pest control products in Canada.

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is a plasticizer and may migrate from baby bottles made from materials used as substitutes for polycarbonate. It has also been measured in plastic toys and other plastic items intended for use by children (Onghena et al. 2016; Simoneau et al. 2012; Bouma and Schakel 2002; Tonning et al. 2009; Janssen and Bremmer 2009).

Subgroup D

Major uses of docusate sodium in Canada include applications in oil and natural gas extraction, food and beverages, drugs, and paints and coatings. A primary function of docusate sodium is as a surface-active agent (Environment Canada 2013). Other applications in Canada include uses in plastic and rubber materials, as a drying agent, adhesive and sealant, in personal care products and cosmetics, fuels and related products, mixtures or manufactured items, cleaning and furnishing care, water treatment, building and construction materials, paper products, inks, toners and colourants, floor coverings, laundry and dishwashing and mining applications (Environment Canada 2013). Docusate sodium (as dioctyl sodium sulfosuccinate) is permitted for use in a limited number of foods, as prescribed in the *List of Permitted Food Additives with Other Accepted Uses*, incorporated by reference into its respective Marketing Authorization issued under the *Food and Drugs Act*. Docusate sodium may be used as a component in the manufacture of food packaging materials, with no direct food contact (personal communication, email from FD, HC, to ESRAB, HC, dated March 15, 2021; unreferenced).

Docusate sodium is also listed in the NHPID with a non-medicinal ingredient role for use as an emulsifying agent, solubilizing agent or wetting agent, as well as with a non-natural health product role because it is not a naturally occurring substance included in Schedule 1 of the *Natural Health Products Regulations*. It is listed in the LNHPD as being present as a non-medicinal ingredient in natural health products in Canada (NHPID [modified 2021]; LNHPD [modified 2021]). Docusate sodium is an active ingredient in prescription and/or non-prescription drugs (primarily laxatives) in Canada and a non-medicinal ingredient in a wide range of products including oral and topical applications and aerosol disinfectants (personal communication, email from TPD, HC, to ESRAB, HC, dated December 5, 2016, and March 18, 2021; unreferenced). Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, docusate sodium (INCI name: diethylhexyl sodium sulfosuccinate) is used in certain cosmetics in Canada such as adhesive, bath products, bleach, cleaners, exfoliant, hair colour, makeup, makeup remover, shampoo, shaving products, styling products and sunless tanning products (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Docusate sodium is a formulant in registered pest control products in Canada.

Table 4-4 summarizes the major uses of the esters in subgroups B, C and D submitted in response to CEPA section 71 surveys (Environment Canada 2009, 2013). Additional uses of the esters in subgroups B, C and D are outlined in Table 4-5.

Table 4-4. Summary of Canadian uses of substances in the Esters Group (subgroups B, C, D) submitted in response to CEPA section 71 surveys

Major uses[a]	Triacetin	Glycerides, C14-22 mono-	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	Texanol	Docusate sodium
Adhesive and sealants	Y	N	Y	Y	Y
Automotive aircraft and transportation	N	N	N	Y	Y
Building or construction materials	N	N	N	Y	Y
Cleaning and furnishing care	N	N	Y	N	Y
Drugs	N	N	N	N	Y
Fabric, textile and leather articles	N	N	Y	N	N
Floor coverings	N	N	Y	Y	Y
Food and beverages	Y	N	N	N	Y
Food packaging	N	Y	N	N	Y
Fuels and related products, mixtures or manufactured items	N	N	N	Y	Y
Ink, toner and colourants	Y	N	Y	N	Y
Laundry and dishwashing	N	N	N	N	Y
Oil and natural gas extraction	N	N	N	N	Y
Paints and coatings	N	N	Y	Y	Y
Paper products, mixtures or manufactured items	N	N	N	N	Y
Personal care and cosmetics	Y	N	N	N	Y
Plastic and rubber materials not otherwise covered	N	N	Y	N	Y
Water treatment	N	N	N	N	Y
Other[b]	Y	N	Y	N	N

Abbreviations: Y, yes; N, no

[a] Non-confidential uses reported in response to CEPA section 71 surveys (Environment Canada 2009, 2013). See survey for specific inclusions and exclusions (schedules 2 and 3).

[b] Other refers to minor uses and/or uses that cannot be disclosed as a result of confidentiality claims.

Table 4-5. Additional uses in Canada for each of the substances in the Esters Group

Use	Subgroup A	Subgroup B	Subgroup C	Subgroup D
Food additive[a]	N	Triacetin Glycerides, C14-22 mono-[b,c]	N	Docusate sodium
Food flavouring[a]	Methyl acetate Methyl hexanoate[c] Propyl acetate Isobutyl acetate[c] Methyl dodecanoate Methyl butanoate	Triacetin	N	N
Food packaging materials[a]	Methyl acetate Propyl acetate Isobutyl acetate[c] 2-Methoxypropyl acetate	Glycerides, C14-22 mono-[c]	2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol	Docusate sodium
Incidental additive[a]	Dimethyl glutarate Tetradecyl tetradecanoate	Triacetin Glycerides, C14-22 mono-[c]	N	N
Internal Drug Product Database as medicinal or non-medicinal ingredients in disinfectant, human or veterinary drug products in Canada[d]	Methyl dodecanoate Tetradecyl tetradecanoate	Triacetin	N	Docusate sodium
Natural Health Products Ingredients Database[e]	Methyl acetate Methyl hexanoate Propyl acetate Isobutyl acetate Methyl dodecanoate Methyl butanoate Dimethyl glutarate Tetradecyl tetradecanoate	Triacetin	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	Docusate sodium
Licensed Natural Health Products	Tetradecyl tetradecanoate	Triacetin	2,2,4-Trimethyl-	Docusate sodium

Use	Subgroup A	Subgroup B	Subgroup C	Subgroup D
Database as medicinal or non-medicinal ingredients in natural health products in Canada[e]			1,3-pentanediol diisobutyrate	
List of Prohibited and Restricted Cosmetic Ingredients[f]	2-Methoxypropyl acetate	N	N	N
Notified to be present in cosmetics, on the basis of notifications submitted under the *Cosmetic Regulations* to Health Canada[f]	Methyl acetate Methyl hexanoate Propyl acetate Isobutyl acetate Methyl dodecanoate Dimethyl glutarate Tetradecyl tetradecanoate	Triacetin	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate Texanol	Docusate sodium
Formulant in pest control products registered in Canada[g]	Methyl acetate Propyl acetate Isobutyl acetate Methyl dodecanoate 2-Methoxypropyl acetate	Triacetin	Texanol	Docusate sodium

Abbreviation: N, this use was not reported for this subgroup

[a] Personal communication, e-mails from FD, HC, to ESRAB, HC, dated December 5, 2016, and March 15, 2021; unreferenced.

[b] "Glycerides, C14-22 mono-" is included in the listings for two approved food additives in Canada. Monoglycerides or mono- and di-glycerides, as set out in Canada's List of Permitted Food Additives (see Subgroup B of section 4 for details).

[c] Personal communication, e-mail from Risk Management Bureau, HC, to ESRAB, HC, dated August 17, 2015; unreferenced.

[d] Personal communication, e-mail from TPD, HC, to ESRAB, HC, dated December 6, 2016, and March 3, 2021; unreferenced.

[e] Personal communication, e-mail from Natural and Non-prescription Health Products Directorate (NNHPD), HC, to ESRAB, HC, dated December 6, 2016, and February 11, 2021; unreferenced.

[f] Personal communication, e-mail from CHPSD, HC, to ESRAB, HC, dated December 8, 2016, and March 5, 2021; unreferenced.

[g] Personal communication, e-mail from RMB, HC, to ESRAB, HC, dated December 12, 2016; unreferenced; personal communication e-mail from Pest Management Regulatory Agency, HC, to ESRAB, HC, dated March 26, 2021; unreferenced.

5. Environmental fate and behaviour

5.1 Environmental persistence

According to models used in ERC (ECCC 2016b), methyl acetate, methyl hexanoate, propyl acetate, isobutyl acetate, methyl butanoate and dimethyl glutarate are expected to persist in air, but not in water, sediment or soil.

According to models used in ERC (ECCC 2016b), docusate sodium is expected to persist in water, sediment and soil, but not in air.

According to models used in ERC (ECCC 2016b), triacetin, methyl dodecanoate, tetradecyl tetradecanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, C14-22 monoglycerides and 2-methoxypropyl acetate are not expected to persist in air, water, sediment or soil.

5.2 Potential for bioaccumulation

Given their low log K_{ow} and low bioconcentration factors (BCF) (ECCC 2016b), methyl acetate, triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, docusate sodium, methyl butanoate, dimethyl glutarate, texanol, and 2-methyoxypropyl acetate are not expected to significantly bioaccumulate in organisms.

Although the log K_{ow} values for methyl dodecanoate, tetradecyl tetradecanoate and C14-22 monoglycerides are moderate to high, the BCFs for these substances are low (ECCC 2016b). As a result, they are not expected to significantly bioaccumulate in organisms.

Although 2,2,4-trimethyl-1,3-pentanediol diisobutyrate has a high log K_{ow} value, given that this substance has a high empirical BCF (5340 L/kg) (ECCC 2016b), it is expected to significantly bioaccumulate in organisms.

6. Potential to cause ecological harm

6.1 Characterization of ecological risk

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

Data on physical-chemical properties, fate (chemical half-lives in various media and biota, partition coefficients, and fish bioconcentration), acute fish ecotoxicity, and chemical import or manufacture volume in Canada were collected from the scientific literature, from available empirical databases (e.g., OECD QSAR Toolbox 2014), and from responses to surveys issued pursuant to section 71 of CEPA, or they were generated using selected (Q)SAR or mass-balance fate and bioaccumulation models. These data were used as inputs to other mass-balance models or to complete the substance hazard and exposure profiles.

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

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

ERC uses a weighted approach to minimize the potential for both over- and under-classification of hazard and exposure and of subsequent risk. The balanced approaches for dealing with uncertainties are described in greater detail in ECCC (2016a). The following describes two of the more substantial areas of uncertainty. Error with empirical or modelled acute toxicity values could result in changes in classification of hazard, particularly metrics relying on tissue residue values (i.e., mode of toxic action), many of which are predicted values from (Q)SAR models (OECD QSAR Toolbox 2014). However, the impact of this error is mitigated by the fact that overestimation of median lethality will result in a conservative (protective) tissue residue value used for critical body residue analysis. Error with underestimation of acute toxicity will be mitigated through the use of other hazard metrics such as structural profiling of mode of action, reactivity and/or estrogen binding affinity. Changes or errors in chemical quantity could result in differences in classification of exposure as the exposure and risk classifications are highly sensitive to emission rate and use quantity. The ERC classifications thus reflect exposure and risk in Canada on the basis of what is estimated to be the current use quantity and may not reflect future trends.

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

The hazard and exposure classifications for the substances in the Esters Group are summarized in Table 6-1.

Table 6-1. Ecological risk classification results for the substances in the Esters Group

Substance	ERC hazard classification	ERC exposure classification	ERC risk classification
Methyl acetate	low	low	low
Triacetin	low	low	low
Methyl hexanoate	low	low	low
Propyl acetate	low	high	low
Isobutyl acetate	low	high	low
Methyl dodecanoate	low	low	low
Docusate sodium	moderate	low	low
Methyl butanoate	low	low	low
Dimethyl glutarate	low	low	low
Tetradecyl tetradecanoate	low	low	low
2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	moderate	low	low
Texanol	low	low	low
C14-22 monoglycerides	low	low	low
2-Methoxypropyl acetate	low	low	low

On the basis of low hazard and low exposure classifications according to information considered under ERC, methyl acetate, triacetin, methyl hexanoate, methyl dodecanoate, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, texanol, C14-22 monoglycerides, and 2-methoxypropyl acetate were classified as having a low potential for ecological risk. It is therefore unlikely that these substances are resulting in concerns for the environment in Canada.

According to information considered under ERC, docusate sodium was classified as having a low exposure potential and a moderate hazard potential, the latter being based on the agreement between the reactive mode of action and elevated ecotoxicity ratio, both of which suggest that this chemical is likely of high potency. However, the potential effects and how they may manifest in the environment were not further investigated due to the low exposure potential of this substance. Considering current use patterns, it is unlikely that docusate sodium is resulting in concerns for the environment in Canada.

According to information considered under ERC, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate was classified as having a low exposure potential and a moderate hazard potential, the latter being based on a moderate potential to cause adverse effects in aquatic food webs given its moderate bioaccumulation potential. The potential effects and how they may manifest in the environment were not further investigated due to the low exposure potential of this substance. It is unlikely that 2,2,4-trimethyl-1,3-pentanediol diisobutyrate is resulting in concerns for the environment in Canada.

According to information considered under ERC, propyl acetate and isobutyl acetate were classified as having high exposure potentials on the basis of relatively large annual import quantities and long half-lives in air. Both substances were classified as having low hazard potentials and as having low potential for ecological risk. Although the current use patterns result in high exposure potentials, considering the low hazard potentials, propyl acetate and isobutyl acetate are unlikely to be resulting in concerns for the environment in Canada.

7. Potential to cause harm to human health

7.1 Subgroup A: Esters of acyclic linear/branched alcohol with linear carboxylic acid

7.1.1 Methyl acetate

Exposure assessment

Environmental media

Methyl acetate is a liquid with a very high vapour pressure. Methyl acetate has been measured in ambient air in four Canadian studies in Windsor, Regina, Halifax and Edmonton (Health Canada 2010a, 2010b, 2012, 2013a). Concentrations of methyl acetate in ambient air from these Canadian studies ranged from below the method detection limit (MDL) to 6.32 $\mu g/m^3$, with geometric mean concentrations ranging from below the MDL to 0.22 $\mu g/m^3$. The highest 95th percentile concentration of methyl acetate in ambient air, based on a large sample size (i.e., > 30), was selected as being representative of general population for ambient air exposure (0.57 $\mu g/m^3$ based on 24-hour samples from the Edmonton study) (Health Canada 2013a).

Methyl acetate was also measured in indoor air in the four Canadian studies noted above. Concentrations of methyl acetate in indoor air ranged from below the MDL to 34.32 $\mu g/m^3$, with geometric mean concentrations ranging from 0.41 $\mu g/m^3$ to 2.4 $\mu g/m^3$ across these Canadian indoor air monitoring studies. The highest 95th percentile indoor air concentration measurement from the four studies was 11.5 $\mu g/m^3$, based on data from the Windsor study collected in 2006 (Health Canada 2010a). This value was used to estimate exposure to the general population of Canada associated with indoor air.

Personal air sampling was also carried out in the Windsor exposure assessment study where adult participants carried a 1.0 L volatile organic compound (VOC) canister, deployed every 24 hours for 5 consecutive days. Concentrations of methyl acetate in personal air samples ranged from below MDL to 10.1 $\mu g/m^3$ in 2005. The geometric means of the personal sampling measurements taken in winter and summer of 2005were 0.72 $\mu g/m^3$ and 2.5 $\mu g/m^3$, respectively, whereas the 95th percentiles for winter and summer measurements were 2.4 $\mu g/m^3$ and 7.0 $\mu g/m^3$, respectively.

Methyl acetate is highly soluble in water. However, a measured Henry's law constant of 1.15×10^{-4} atm m^3/mol indicates that volatilization from water surfaces is expected (HSDB 1983-). No data measuring methyl acetate in water in Canada were identified. Concentrations in surface water were estimated with the New Substances Assessment and Control Bureau (NSACB) Environmental Assessment Unit (EAU) Drinking Water Spreadsheets using the industrial release scenario (Health Canada 2015a). This is considered a conservative estimate of potential presence in water, as much of methyl acetate is likely to volatilize.

Methyl acetate was not identified in soils or dust studies in Canada or internationally. Methyl acetate is expected to have a very high mobility in soil and is expected to volatilize from moist and dry soil surfaces.

Food

Methyl acetate may be used as a component in the manufacture of food packaging materials with no direct food contact. Therefore, dietary exposure is not expected (personal communication, emails from FD, HC, to ESRAB, HC, dated December 5, 2016, and March 15, 2021; unreferenced).

Methyl acetate has been measured in several foods primarily as a result of its natural occurrence. In addition, methyl acetate may be used as a flavouring agent in food. The Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) evaluated esters of aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids (including methyl acetate) using the Procedure for the Safety Evaluation of Flavouring Agents which concluded that methyl acetate presents "no safety concern" based on currently levels of intake as a food flavouring agent (WHO 1998). As part of this evaluation, JECFA estimated the per capita intake of methyl acetate in the United States to be 110 μg/person/day (1.8 μg/kg bw/day based on an average body weight of 60 kg for the general population). The intake is estimated using a maximized survey-derived daily intake (MSDI) approach, based on the reported annual production amount of methyl acetate in the United States (International Organization of the Flavour Industry 1995, as cited in WHO 1998; US National Academy of Sciences 1987, as cited in WHO 1998).

The potential dietary exposure from possible food uses of methyl acetate as a flavouring agent is expected to be small relative to intakes of this substance from its natural occurrence in food. Stofberg and Grundschober (1984) calculated consumption ratios for various flavouring agents, comparing the average intakes of the added flavouring agent to quantities consumed as a result of their natural occurrence in foods. They indicated that this substance is primarily consumed through its natural occurrence in food rather than through its addition as a flavouring agent.

In order to characterize the potential exposure of the general population from dietary sources of methyl acetate from its natural presence in food, quantitative exposure estimates were derived (personal communication, e-mail from FD, HC, to ESRAB, HC, dated December 8, 2017). Methyl acetate is listed in the Volatile Compounds in Food (VCF) database as being present in a range of foods, including apple, banana, cherry, citrus, guava, grapes, melon, nectarines, pineapple, tomato, vinegar, beer and sherry, (Nijssen et al. 1963-2016). Quantitative exposure estimates were derived from consumption data for comparable food categories from the Canadian Community Health Survey (CCHS cycle 2.2) all-persons consumption of defined food categories (Health Canada 2015). Analytical occurrence values sourced from the VCF database and the scientific literature were applied to the consumption of each food category as appropriate. The dataset of methyl acetate occurrence was sufficiently detailed for a wide variety of foods such that all-persons consumption was considered appropriate. Estimated exposures to methyl acetate from its natural occurrence in food are shown in Table 7-1. The highest 90th percentile dietary exposure of the general population was 33.1 μg/kg bw/day based on the 1- to 2-year-old age group.

Table 7-1. Estimated exposure to methyl acetate from natural occurrence in food

	Estimated exposure (μg/kg bw/day) (based on all persons consumption)							
Age group	**0–5 months**	**6–11 months**	**1 year**	**2–3 years**	**4–8 years**	**9–13 years**	**14–18 years**	**19+ years**
Mean	0.0	8.6	14.2	13.5	10.1	6.7	5.0	8.9
90th percentile	0.0	28.1	33.1	28.3	21.9	15.0	11.2	12.1

General population exposure to methyl acetate from environmental media and food (based on 90th percentile dietary exposure) ranged from 6 μg/kg bw/day to 43 μg/kg bw/day (refer to Appendix B, Table B-1). On the basis of available information, the predominant sources of exposure to methyl acetate from environmental media and food for the general population are considered to be diet and indoor air. It is expected that most dietary exposure to methyl acetate results from its natural occurrence in foods.

Products available to consumers

Methyl acetate functions as a perfume agent and solvent in cosmetics (European Commission 2008-) and is found in cleansers, exfoliants, eye makeup, moisturizers, face masks, nail polishes and nail polish removers in Canada (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced).

Methyl acetate has a very high vapour pressure and is expected to have low retention time on the skin for products that are not washed off. Although dermal exposure is expected to contribute to the overall exposure during use of the product, the primary route of exposure is considered to be inhalation.

Table 7-2 summarizes the estimates of air concentrations associated with the use of cosmetics containing methyl acetate for relevant age groups. These values represent the average air concentration over a 24-hour time period, considered relevant for comparison to the reference air concentration. Air concentration values were not estimated for rinse off cosmetics due to limited inhalation exposure potential. 24-Hour average air concentrations associated with use of makeup was considered to be less than 0.03 mg/m^3.

Table 7-2. Estimated inhalation exposures to methyl acetate from the use of certain cosmetics

Product scenario	Methyl acetate conc.[a]	Mean conc. on day of exposure[b] (mg/m^3)
Nail polish (19+ years)	30%	4.3
Nail polish (2-3 years)	30%	1.4
Nail polish remover (19+ years)	100%	9
Nail polish remover (2-3 years)	100%	3.6

Abbreviation: conc., concentration

[a] Personal communication, emails from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced.

[b] Air concentration estimates were derived using Consumer Exposure Web Model (ConsExpo Web 2016); see Appendix C-3 for information regarding input parameters.

In addition to cosmetics, methyl acetate is used in a variety of other products available to consumers that may result in exposure to the general population in Canada. Many of these products are aerosols, including kitchen cleaning/polishing products (SDS 2015a), automotive products (e.g., paint [SDS 2019], tire cleaning sprays [SDS 2014a], adhesive removers [SDS 2014b]), and aerosol adhesives (SDS 2018b). Non-aerosol products include paint removers (SDS 2018a), gutter sealants (SDS 2011), construction, roof and landscaping adhesives (SDS 2018c), garage floor coating products (SDS 2015b) and general purpose adhesives (SDS 2015c). Potential air concentrations associated with the use of these products available to consumers were estimated using ConsExpo Web (ConsExpo 2016) and are summarized in Table 7-3. As with cosmetics, the 24-hour time period was considered relevant for comparison to the reference concentration.

Table 7-3. Estimated mean 24-hour air concentrations for methyl acetate from the use of products available to consumers

Product scenario	Methyl acetate conc. in product	24-Hour air conc. on day of exposure[a] (mg/m^3)
Aerosol cleaner/polish	2.5–10%	0.73
Aerosol automotive spray paint (e.g., tire rims)	5–26%	34
Aerosol spray tire cleaner (automotive)	60%	6
Trigger spray tire cleaner	60%	7.4
Aerosol adhesive remover (automotive)	80%	0.6
Aerosol adhesive (automotive/household)	40%	52
Construction adhesive; joint assembly	1–5%	10
Tube glue	50–100%	3.4 - 6.4
Aerosol lubricant	10%	0.94
Paint remover[b] - small project (lower/higher ventilation rate) - large project (lower/higher ventilation rate) - bathtub	70%	 79 / 246[c] 712 / 2153[c] 1136
Garage floor coating	15% (mix/load) 10% (application)[d]	44

Abbreviation: conc., concentration

[a] Air concentration estimates were derived using Consumer Exposure Web Model (ConsExpo Web 2016); see Appendix C-3 for information regarding input parameters as well as peak and event air concentrations.

[b] Paint remover scenarios were divided into several scenarios: two sizes of projects (small and large), each under two ventilation conditions and a bathtub scenario. Details are provided in Appendix C-3.

[c] Two air concentration values represent the two ventilation scenarios.

[d] 15% represents the amount of substance in one component of a two-component product; once mixed, the applied product contains 10% of substance.

In addition to the products referred to above, methyl acetate was reported to be emitted from building materials in Canada, including caulking, hardwood flooring, medium density fiberboard and oriented strand board (Won and Lusztyk 2011). Chamber air concentrations ranged from 0.03 µg/m^3 to 98.2 µg/m^3 at 24 hours (Won and Lusztyk 2011). This source of exposure is considered to be addressed by the characterization of exposure from other scenarios in Table 7-3 (e.g., aerosol cleaner polish), which result in concentrations likely higher than those emitted from building materials.

Health effects assessment

The health effects characterization of methyl acetate in this assessment was informed by the European Union Risk Assessment Report for methyl acetate (EU RAR 2003). A literature search was conducted from the year prior to the EU RAR (i.e., January 2002) to December 2020. No health effects studies that could impact the risk characterization conducted in the EU RAR (i.e., result in different critical endpoints or lower points of departure than those stated in EU RAR 2003) were identified for methyl acetate. The main metabolite of methyl acetate, methanol, was reviewed internationally by ECHA (2015a, 2016a) and the US EPA (2013a, 2013b); these reviews also informed the health effects assessment of methyl acetate. A literature search for methanol was conducted up to the period of April 2020 and no studies that could result in a different health effects assessment from that of these agencies was identified. Methanol was reviewed in the draft screening assessment for the Alcohols Group under the CMP (ECCC, HC 2022).

The EU RAR (2003) provided a summary of the toxicokinetics of methyl acetate. After absorption, methyl acetate undergoes rapid hydrolysis to form methanol and acetic acid by non-specific esterases present in the blood and tissues. The systemic availability of methyl acetate is low. From the available *in vitro* data, the half-life of methyl acetate in blood was estimated to be 2 to 3 hours in rats and about 2 hours in humans. Immediately after a 6-hour inhalation exposure to rats (2000 parts per million [ppm] or 6040 mg/m^3), blood concentrations were determined to be below the limit of quantification (less than 4.6 mg/L), indicating hydrolysis and high clearance of the substance (EU RAR 2003).

Repeated-dose toxicity

The EU RAR (2003) indicates that there are no repeated-dose studies available for methyl acetate following oral or dermal exposure, and no subchronic or chronic inhalation studies were identified. Data from the main metabolite of methyl acetate, methanol, have been reviewed by the EU in its assessment of methyl acetate. However, inhalation studies in which animals were exposed to methanol were deemed to be of lower quality than a short-term inhalation study for methyl acetate presented below (EU RAR 2003).

A short-term repeated-exposure study in which Sprague-Dawley rats were exposed to methyl acetate via the inhalation route was identified by the EU RAR (2003) as the basis for their selection of critical effect level for both local and systemic effects. In this study, test animals (10/sex/dose) were exposed to methyl acetate (nose-only) at concentrations of 0, 75, 350 or 2000 ppm (mean analytical concentrations 79, 335 and 2018 ppm, equivalent to 227, 1057, and 6040 mg/m^3, respectively), 6 hours daily, 5 days per week for 28 days. A no-observed-adverse-effect concentration (NOAEC) of 350 ppm (1057 mg/m^3) was identified by the EU RAR (2003) based on observed degeneration/necrosis of the rat olfactory mucosa at the next concentration of 2000 ppm (6040 mg/m^3). These were considered to be site-of-contact effects. With respect to systemic effects, the low and mid-concentrations were associated with reduced cholesterol levels and changes in adrenal and thymus weights. However, these changes were qualified as “slight” and only occurred in female animals. At the highest concentration, there were effects on both sexes, including decreased body weight and food consumption, decreased cholesterol levels, increased alanine aminotransferase activity, increased adrenal weight, increased diuresis, decreased thymus weights, and increased levels of erythrocytes, hemoglobin, hematocrit, and calcium (HMR 1999a, as cited in EU RAR 2003). Although no morphological changes were observed, the EU RAR (2003) indicated that the aforementioned findings represented minimal adverse effects related to treatment with methyl acetate and derived a systemic NOAEC of 1057 mg/m^3 on the basis of the effects observed at the next concentration of 6040 mg/m^3.

No chronic, repeated-dose exposure studies are available for methyl acetate.

Reproductive/developmental toxicity

There are no data available on the reproductive toxicity of methyl acetate. Due to the rapid hydrolysis of the substance, the EU RAR (2003) considered it justified to base the characterization of reproductive and developmental effects of methyl acetate on its main metabolite, methanol, for which developmental effects have been demonstrated in rodents (EU RAR 2003).

The US EPA (2013a) evaluated various methanol toxicity studies comprising data from different species and endpoints and derived a reference dose (RfD) of 2 mg/kg bw/day and a reference concentration (RfC) of 20 mg/m^3 based on developmental effects. The RfD and RfC values were calculated for a population with a background blood level of methanol at or below 2.5 mg/L as a result of metabolism and consumption of foods (fruits and vegetables) with naturally occurring methanol. Developmental effects included skeletal (cervical rib or supernumerary rib) malformation, cleft palate, and exencephaly in mice pups in the absence of any maternal toxicity, reduced brain weight in adult and developing rat pups, and indications of developmental effects in monkeys following repeated-dose inhalation exposure (Kavet and Nauss 1990; Burbacher et al. 1999a, 1999b, 2004a, 2004b; Rogers et al. 1993; NEDO 1987; Fisher et al. 2000, OECD 2004). The US EPA indicated that these studies showed consistent developmental effects at similar doses in mice and rats. Notably, the biological significance of these effects is considered relevant to humans as increase in SNR and decrease in brain weight may occur in humans and are considered adverse effects (US EPA 2013a, 2013b; Chernoff 2004). Due to the developmental nature of the effects, the reference dose and reference concentration are considered relevant to both short- and long-duration exposures. The US EPA noted that although there are uncertainties regarding the relevance to humans of the effects seen in rodents, there was sufficient evidence of potential developmental effects in primates, as well as a lack of knowledge about the metabolism of methanol in human infants, to justify the use of the rodent studies to determine inhalation and oral points of departure. The RfD and RfC values for methanol (2 mg/kg bw/day and 20 mg/m^3, respectively) were adjusted to reflect exposure to methyl acetate (4.6 mg/kg bw/day and 46 mg/m^3, respectively) assuming methyl acetate is immediately degraded to methanol at a molar ratio of 1.

The ECHA Committee for Risk Assessment (RAC) determined that based on available information there was insufficient evidence for classifying methanol for developmental toxicity in humans (ECHA 2015a). They concluded that the most relevant endpoint for general population exposure via the inhalation and dermal routes was transient neurological effects and supported a derived-no-effect level (DNEL) of 43.3 mg/m^3 and 6.66 mg/kg bw/day for these routes of exposure based on existing EU indicative occupational exposure limit values. ECHA subsequently proposed an oral DNEL of 88 mg/kg bw to be protective of acute methanol toxicity by ingestion. This DNEL was based on significantly reduced visual acuity at 260 mg/kg bw (ECHA 2016b).

Short-duration exposures to airborne methyl acetate in humans has been reported to result in irritation of the eyes, nose, throat, and trachea from exposure to approximately 15000 mg/m^3 (Reus 1933, as cited in EU RAR 2003). Other effects such as visual disorders, central nervous system symptoms, difficulties breathing, etc, have also been reported, although these studies did not contain sufficient exposure information and/or were related to product mixtures.

The main metabolite of methyl acetate, methanol, has been reported to cause dizziness, headache, nausea, insomnia, blurred vision and conjunctivitis (US EPA 2005). In a workplace study, exposure to mean air concentration of 1060 ppm (1400 mg/m^3) of methanol was reported to cause significantly higher frequencies of headaches, nausea, dizziness and blurred vision in school teachers (Frederick et al. 1984). In another study, workers reported eye irritation following 25-minute exposure to 1025 ppm (1300 mg/m^3) of airborne methanol (NIOSH 1981). The methanol air concentrations resulting in these effects were used to estimate air concentrations of methyl acetate (assuming methyl acetate is immediately degraded to methanol at a molar ratio of 1) resulting in estimates of 2990 mg/m^3 to 3220 mg/m^3 (based on 1300 mg/m^3 and 1400 mg/m^3 of methanol, respectively).

Genotoxicity

The EU concluded that there is no concern with respect to genotoxicity for methyl acetate (EU RAR 2003). Methyl acetate was found to be negative in bacterial mutation tests, in the absence or presence of metabolic activation (EU RAR 2003). Negative results were also reported *in vivo* in a rat bone marrow micronucleus test in which animals (5/sex/group) were exposed through inhalation at doses of 75, 350, and 2000 ppm for 6 hours, 5 days per week for 28 days (HMR 1999b, as cited in EU RAR 2003). The genotoxicity potential of methanol has been reported to be negative in the majority of *in vitro* and *in vivo* assays (IPCS 1997; NTP 2004; OECD 2004).

Carcinogenicity

The EU RAR (2003) concluded that “no available data give relevant concern for carcinogenicity following exposure to methyl acetate.” There are no data on the carcinogenic potential of the metabolite acetic acid (EU RAR 2003). Methanol has not been classified as a carcinogen by the US EPA, International Agency for Research on

Cancer (IARC) or the National Toxicology Program (NTP) (Cruzan 2009; IARC 2018). Based on this information and the absence of evidence for a mutagenic potential for methyl acetate, the EU concluded that “methyl acetate is not suspected to be carcinogenic” (EU RAR 2003).

Characterization of risk

Methyl acetate has been reviewed by the EU. The EU RAR (2003) concluded that there is no evidence that methyl acetate may be associated with carcinogenic or genotoxic effects in the available empirical data for methyl acetate and its main metabolite, methanol.

Since the only reported effects observed following inhalation exposure to methyl acetate were site-of-contact effects and minor systemic effects (likely related to a stress response) at high concentrations, a quantitative risk characterization using a methyl acetate endpoint was not considered in this assessment. No reproductive or developmental toxicity studies were identified for methyl acetate.

Although developmental studies have not been identified for methyl acetate, potential developmental effects are associated with the main metabolite, methanol, and are considered in this assessment. The RfD and RfC for oral and inhalation exposure to methanol derived by the US EPA were 2 mg/kg bw/day and 20 mg/m^3, respectively. The RfD and RfC for methanol were adjusted on the basis of differences in molecular weight (assuming that, following exposure to methyl acetate, it is immediately degraded to methanol at a molar ratio of 1). When the methanol RfD and RfC values are adjusted to reflect exposure to methyl acetate, the resulting values are 4.6 mg/kg bw/day and 46 mg/m^3, respectively. The adjusted values were compared to estimated exposures of Canadians to methyl acetate.

The predominant routes of environmental exposure to methyl acetate for the general population are through natural occurrence in food and indoor air. Inhalation exposure may also occur as a result of the use of products available to consumers.

Table 7-4 presents relevant exposure values or air concentrations for methyl acetate compared to methanol RfC and RfD (adjusted for methyl acetate). These values were used in the characterization of human health risk from exposure to methyl acetate.

Table 7-4. Comparison of exposure or estimated mean 24-hour air concentrations with RfC/RfD for methanol (adjusted for methyl acetate)

Scenario	Exposure (mg/kg bw/day) or estimated mean 24-hr air concentrations (mg/m^3)[a]	Does exposure exceed RfD or RfC for methanol (adjusted based on exposure to methyl acetate)?
Environmental media and natural occurrence in food (oral chronic; 1-year-old)	0.043 mg/kg bw/day	No
Nail polish (30%)	4.3 mg/m^3	No
Nail polish remover (100%)	9 mg/m^3	No
Aerosol stainless steel polish (10%)	0.73 mg/m^3	No
Aerosol spray paint (automotive; 26%)	34 mg/m^3	No
Aerosol spray tire cleaner (automotive; 60%)	6 mg/m^3	No
Trigger spray tire cleaner (automotive; 60%)	7.4 mg/m^3	No
Aerosol adhesive remover (automotive; 80%)	0.6 mg/m^3	No
Aerosol adhesive (automotive/household; 40%)	52 mg/m^3	Yes
Construction adhesive – joint assembly (5%)	10 mg/m^3	No
Tube glue (100%)	6.4 mg/m^3	No
Aerosol lubricant (10%)	0.94 mg/m^3	No
Paint removers (70%): - small project - large project - bathtub	 79 – 246 mg/m^3 712 – 2153 mg/m^3 1136 mg/m^3	 Yes Yes Yes
Garage floor coating; (product: 15%; during application: 10%)	44 mg/m^3	No

Abbreviations: RfD, reference dose; RfC, reference concentration; hr, hour

[a] Air concentration values for methyl acetate reflect mean 24-hour concentrations on the day of exposure; the mean 24-hour air concentration considered relevant for comparison to the reference concentration derived from methanol.

Exposure to methyl acetate from environmental media and its natural occurrence in food is less than the RfD for methanol (adjusted for methyl acetate) and therefore is not considered to be of concern for human health. The contribution of intake from the potential use of methyl acetate as a flavouring agent in foods would be minimal compared to the total exposure from environmental media and natural occurrence in food.

The general population of Canada may also be exposed to methyl acetate via the inhalation route when using various products available to consumers containing the substance, including nail products, cleaning products, automotive products (e.g., aerosol paints, aerosol adhesives), adhesives (e.g., construction adhesives, tube adhesives), lubricants, paint removers, and floor coatings. All calculated 24-hour average air concentrations associated with the use of products available to consumers, except aerosol adhesives and paint removers, are below the RfC for methanol (adjusted for exposure to methyl acetate) and therefore are not considered to be of concern. In the case of paint remover (three scenarios), the estimated 24-hour average air concentrations are estimated to be above the RfC for methanol (adjusted to methyl acetate) and, as such, are of potential concern.

It is noted that concentrations higher than 15 000 mg/m^3 for airborne exposure to methyl acetate were observed to lead to irritation. Furthermore, concentrations higher than 1025 ppm (1300 mg/m^3) for airborne exposure to methanol (equivalent to approximately 2990 mg/m^3 methyl acetate) were observed to lead to irritation and dizziness following short-duration exposures in workers (US EPA 2005; Frederick et al. 1984; NIOSH 1980). Inhalation exposures for paint or varnish remover scenarios which lead to mean event or peak concentrations of methanol higher than this value may be self-limited by the discomfort that the user may feel while exposed to the product.

7.1.2 Methyl hexanoate

Exposure assessment

Methyl hexanoate was detected in fewer than 10% of the samples in two indoor air studies conducted in Canada. In the national Canadian indoor air study conducted in 2009-2011 as part of cycle 2 of the Canadian Health Measures Survey (CHMS), methyl hexanoate was detected in only 5% of the samples (95th percentile concentration was 0.18 µg/m^3) (personal communication, e-mail from Environmental Health Science and Research Bureau (EHSRB), HC, to ESRAB, HC, dated December 2012; unreferenced). In a study of indoor air in homes in Quebec City (sampling between November 2008 and March 2010), methyl hexanoate was only detected in 8% of the samples (maximum reported concentration of 0.33 μg/m^3) (Won and Lusztyk 2011).

Measured concentrations of methyl hexanoate in ambient air, water or dust were not identified in Canada.

General population exposure to methyl hexanoate from environmental media (indoor air) ranged from 0.06 μg/kg bw/day to 0.17 μg/kg bw/day.

Methyl hexanoate has been evaluated by JECFA as a food flavouring agent which concluded that the substance posed “no safety concern” based on current levels of intake when used as a flavouring agent (WHO 2009). In the absence of data on actual use, if any, in Canada, the per capita intake estimates for the US population derived by JECFA of 41 μg/person/day (1 µg/kg bw/day based on an average body weight of 60 kg for the general population) is an acceptable estimate of possible Canadian dietary exposure to methyl hexanoate from its potential use as a food flavouring agent for the general population (1 year of age and older) (WHO 2009; personal communication, email from FD, HC, to ESRAB, HC, dated December 5, 2016; unreferenced).

Methyl hexanoate was identified in cosmetics, specifically nail moisturizing products, at concentrations of up to 10% (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Dermal exposure to methyl hexanoate was estimated assuming an application scenario of nail polish remover. The highest estimated exposure via the dermal route was estimated to be 5.4 mg/kg bw/day for the 9- to 13-year-old age group.

This substance was not reported to be imported or manufactured in Canada, and therefore releases from industrial sources are not expected.

Health effects assessment

A literature search was conducted up to December 2020. Only limited health effects information was identified. Methyl hexanoate showed negative results in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 at concentrations of 8 µg/plate to 5000 µg/plate with and without metabolic activation (Anonymous 1996, as cited in ECHA c2007-2017d).

Following absorption, it is expected that methyl hexanoate undergoes hydrolysis by non-specific esterases present in the blood and tissues to form hexanoic acid (CAS RN 142-62-1) and methanol (CAS RN 67-56-1). Information on the two metabolites was examined to inform the human health assessment of methyl hexanoate.

Methyl hexanoate is also structurally similar to another ester of its subgroup, methyl dodecanoate (CAS RN 111-82-0). As methyl dodecanoate was identified as a potential analogue for methyl hexanoate, information for methyl dodecanoate was also examined to inform the human health assessment of methyl hexanoate.

Hexanoic acid

Repeated-dose toxicity

Hexanoic acid was reviewed by the OECD as part of the Aliphatic Acids Category assessment. In the OECD report (2014), it was concluded that repeated oral exposure (via gavage or diet) to aliphatic acids (including hexanoic acid) did not result in systemic toxicity, with no-observed-adverse-effect levels (NOAELs) greater than 1000 mg/kg bw/day. The OECD identified docosanoic acid (CAS RN 112-85-6) as the closest structural analogue with data to hexanoic acid. In a combined repeated-dose and reproductive/developmental toxicity test, rats (13/sex/group) were administered docosanoic acid by oral gavage at doses of 0, 100, 300, or 1000 mg/kg/day. For males, the exposure period was 42 days; for females, the exposure period was from 14 days prior to mating to day 3 of lactation (minimum of 39 days of exposure). The NOAEL was identified to be 1000 mg/kg bw/day on the basis that no deaths or changes in general condition, no changes in body weight gain or food consumption, and no adverse histopathological, hematological or biochemical effects occurred at any of the doses tested (OECD 2014).

No inhalation or dermal studies were identified.

Reproductive/developmental toxicity

The OECD (2014) identified docosanoic acid as the closest structural analogue with data to hexanoic acid. In the combined repeated-dose and reproductive/developmental toxicity test described earlier for docosanoic acid, no reproductive effects were identified up to the highest dose tested. The NOAEL for reproductive toxicity was greater or equal to 1000 mg/kg bw/day in males and females. There were also no effects on developmental parameters. The NOAELs for maternal and developmental toxicity were greater or equal to 1000 mg/kg bw/day (OECD 2014).

In the OECD report (2014), no effects on fertility or reproductive organs, and no developmental effects were observed in studies for the aliphatic acids examined in the report. The OECD indicated that the weight of evidence supports the lack of reproductive and developmental toxicity potential of the aliphatic acids.

Genotoxicity

Negative results were reported in an Ames test for hexanoic acid using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, with and without metabolic activation (OECD 2014). According to OECD (2014), aliphatic acids are not mutagenic or clastogenic *in vitro* or *in vivo*. The OECD stated that “the weight of evidence indicates that members of the aliphatic acids category [such as hexanoic acid] are not anticipated to be genotoxic.”

Methanol

Methanol was reviewed in the draft screening assessment for the Alcohols Group under the CMP (ECCC, HC 2022), and information is also summarized in section 7.1.1 (Health Effects Assessment) of this document. Using a similar approach to that presented in section 7.1.1, the RfC and RfD values for methanol derived by the US EPA (20 mg/m^3 and 2 mg/kg bw/day, respectively) were adjusted to reflect exposure to methyl hexanoate (resulting in adjusted values of 80 mg/m^3 and 8 mg/kg bw/day, respectively), assuming methyl hexanoate is immediately degraded to methanol at a molar ratio of 1.

Methyl dodecanoate

The assessment of this substance is presented in section 7.1.5. Methyl dodecanoate was considered by the OECD (2013) to have a “low hazard profile” based on the available dataset. There were no treatment-related adverse effects observed in a combined oral repeated-dose and reproductive/developmental toxicity screening test up to and including the limit dose[6] of 1000 mg/kg bw/day. Also, methyl dodecanoate was considered non-genotoxic *in vitro*. The OECD classified this substance as low priority for further work.

Characterization of risk

Following absorption, it is expected that methyl hexanoate undergoes hydrolysis by non-specific esterases present in the body to form hexanoic acid and methanol.

Hexanoic acid has been reviewed by the OECD (2014) as part of the Aliphatic Acids Category assessment. Repeated-dose oral (gavage or diet) exposure to aliphatic acids did not result in systemic toxicity. In addition, the OECD indicated that the weight of evidence supports the lack of reproductive and developmental toxicity potential of the aliphatic acids category. In addition, according to OECD (2014), members of the aliphatic acids category are not expected to be genotoxic.

Methanol is formed through hydrolysis of methyl hexanoate. Potential developmental effects associated with methanol are considered in this assessment. The RfC and RfD derived by the US EPA for inhalation and oral exposure to methanol (20 mg/m^3 and 2 mg/kg bw/day, respectively) were adjusted to reflect exposure to methyl hexanoate and resulted in values of 80 mg/m^3 and 8 mg/kg bw/day (assuming methyl hexanoate is immediately degraded to methanol at a molar ratio of 1). The reported maximum indoor air concentration (0.33 μg/m^3) and estimated exposure of the general population via indoor air and possible use as food flavouring agent is 0.001 mg/kg bw/day. The use of methyl hexanoate in cosmetics resulted in an exposure estimate of 5.4 mg/kg bw/day

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[6] Limit dose is defined as the highest dose which should be used in the absence of a maximum tolerated dose (MTD), and is typically set at 1000 mg/kg bw/day (OECD 2013).

for the 9- to 13-year-old age group assuming all substance is absorbed via the dermal route. All exposure values are below the above noted methanol reference values (adjusted for methyl hexanoate exposure).

No genotoxic or carcinogenic potential has been observed for methanol.

Methyl hexanoate is structurally similar to methyl dodecanoate, which was considered by the OECD (2013) to have a “low hazard profile.”

Considering the available information for the metabolites and the analogue methyl dodecanoate, the risk to human health from exposure to methyl hexanoate is considered low.

7.1.3 Propyl acetate

Exposure assessment

As propyl acetate is considered to be of low hazard potential (see health effects assessment below), quantitative estimates of exposure to the general population were not derived. This section provides general information on exposure to propyl acetate.

Measured concentrations of propyl acetate in ambient air, indoor air, water or dust were not identified in Canada. Given its large volume of import into Canada (> 3 341 000 kg) and its high vapour pressure and water solubility, propyl acetate may be present in air and water. Volatilization from water surfaces is expected based on the value for Henry's law constant (2.18×10^{-4} atm-m^3/mol).

Propyl acetate has been evaluated as a flavouring substance by JECFA, which concluded that the substance posed no safety concern when used as a flavouring agent (WHO 1998). In Canada, propyl acetate has been identified for use in food packaging materials as a solvent in the manufacture of polyethylene, nitrocellulose, wax, and laminate-based products and as a component in inks and pigment-based materials, all with no potential for direct food contact (personal communication, email from FD, HC, to ESRAB, HC, dated March 15, 2021; unreferenced).

Propyl acetate was reported as an ingredient in a large number of cosmetic products available to consumers in Canada, primarily nail polishes. Reported concentration ranges for nail polishes are from less than 0.1% to 30% to 100% (personal communication, emails from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced).

Propyl acetate was also found in a range of products available to consumers in Canada including aerosol paints, automotive paints and adhesive products (SDS 2013a, 2015d, 2017a).

Health effects assessment

Propyl acetate has been reviewed by the OECD (2008), and this review was used to inform the health effects characterization in this assessment.

A literature search was conducted from the year prior to the OECD Screening Information Dataset (SIDS) Initial Assessment Report (SIAR) (January 2007) to December 2020. An additional report of a study examining reproductive toxicity was identified.

The OECD identified ethyl acetate (CAS RN 141-78-6) and *n*-butyl acetate (CAS RN 123-86-4) as structural analogues for propyl acetate. Both ethyl acetate and *n*-butyl acetate have similar toxicity profiles. However, effect levels are lower for ethyl acetate than for *n*-butyl acetate, and according to the OECD, it is expected that propyl acetate would have effect levels between those of these two substances (OECD 2008). Following absorption, propyl acetate is also rapidly hydrolyzed to *n*-propyl alcohol (CAS RN 71-23-8). Information on this substance was also examined by the OECD.

Repeated-dose toxicity

There were no repeated-dose inhalation studies available for propyl acetate. However, inhalation studies were available for *n*-propyl alcohol and the analogue substances, ethyl acetate and *n*-butyl acetate. The reported health effects of ethyl acetate and *n*-butyl acetate were primarily site-of-contact effects, generally at high concentrations. According to the OECD, similar site-of-contact effects on the nasal epithelium are expected in response to repeated inhalation exposure to propyl acetate.

For *n*-propyl alcohol, there was no mortality, no changes in organ weights, no changes in clinical chemistry, hematology or histopathology results, and no gross or microscopic lesions observed in Sprague-Dawley rats exposed via inhalation in a short-term (9 days), repeated-dose study (OECD 2008).

In a repeated-dose study conducted in rats exposed to ethyl acetate vapour for 6 hours/day, 5 days/week, for 13 weeks, the critical effect level and corresponding hazard endpoint was a lowest-observed-adverse-effect concentration (LOAEC) of 350 ppm (1280 mg/m^3), the lowest dose tested, based on necrosis of the olfactory epithelium in some rats. At the two highest dose levels (750 ppm or 2750 mg/m^3 and 1500 ppm or 5490 mg/m^3), all rats exhibited necrosis of the olfactory epithelium, as well as decreased food consumption, decreased body weight gains and a transient decrease in alertness to an auditory stimulus (OECD 2008).

Another subchronic inhalation study was conducted in rats with *n*-butyl acetate. Animals were exposed to *n*-butyl acetate vapour at 0, 500, 1500 or 3000 ppm (0, 2350, 7050 or 14100 mg/m^3) for 6 hours/day, 5 days/week, for 13 weeks. The critical effect level was identified as a NOAEC of 500 ppm (2350 mg/m^3) on the basis of multiple effects including signs of nasal irritation and necrosis of the olfactory epithelium observed in 10/20 rats (4 males and 6 females) exposed to 1500 ppm and in all animals at the highest concentration. Signs of stomach irritation were observed in females at the highest concentration tested. Other effects observed were nasal discharge of porphyrin and decreased food consumption at all concentrations, decreased body weight gains and increased salivation at 3000 ppm, reductions in mean body weights and minimal reductions in activity at 1500 ppm and 3000 ppm, higher testes weights at 1500 ppm and 3000 ppm, higher adrenal weights in females at 1500 ppm and both sexes at 3000 ppm, and lower spleen and higher lung weights in males at 3000 ppm (OECD 2008).

On the basis of the results of subchronic neurotoxicity studies in rats exposed to ethyl acetate and *n*-butyl acetate via inhalation, the OECD concluded that both substances show only minimal neurological effects. No neurotoxicity was observed in a subchronic study conducted using *n*-butyl acetate up to the highest tested concentration of 3000 ppm (14 100 mg/m^3). The NOAEC was thus set at 3000 ppm (14 100 mg/m^3) (OECD 2008). In the case of ethyl acetate, the NOAEC for subchronic neurotoxicity was 750 ppm (2750 mg/m^3) on the basis of the decrease in motor activity observed in exposed female rats at 1500 ppm (5490 mg/m^3) (OECD 2008).

Reproductive/developmental toxicity

No reproductive and/or developmental toxicity studies were available for propyl acetate. This substance is currently listed on ECHA’s Community Rolling Action Plan (CoRAP) to be evaluated (proposed to begin in 2022) due to concerns of wide dispersive use, exposure of workers, and “reprotoxic” potential identified on the basis of available data on propyl alcohol and *n*-butyl acetate.

On the basis of the data for the metabolite propyl alcohol and the analogue *n*-butyl acetate, the OECD found that inhalation of propyl acetate has the potential to induce reproductive and developmental toxicity (reversible changes in male fertility, fetal malformations and variations), but only at very high concentrations.

In one study identified for *n*-propyl alcohol, rats (18/sex/concentration) were exposed at concentrations of 0, 3500 or 7000 ppm (0, 8610 or 17 200 mg/m^3) for 7 hours/day, 7 days/week, for 62 days, prior to being mated with unexposed rats of the opposite sex. The NOAEC for female fertility was 7000 ppm (17 200 mg/m^3), and the NOAEC for male fertility was 3500 ppm (8610 mg/m^3) on the basis of a marked reduction in fertility in males exposed at the highest concentration (reversed after a 13-week recovery period) (OECD 2008).

For *n*-butyl acetate, a report of a two-generation toxicity study in rats exposed via inhalation to 0, 750, 1500, and 2000 ppm (equivalent to approximately 0, 3563, 7126, and 9502 mg/m^3) was identified (Anonymous 2010, as cited in ECHA c2007-2020a). No treatment-related adverse effects on reproduction were observed up to the highest tested concentration of 2000 ppm (9502 mg/m^3). Furthermore, in a subchronic study described earlier (OECD 2008), no effects on male fertility (no difference in testicular spermatid head counts or epididymal spermatozoa counts relative to controls) were observed at any of the concentrations tested (up to 14 100 mg/m^3). In another study in which female rats were exposed to *n*-butyl acetate for 7 hours/day, 5 days/week, for 3 weeks prior to mating with unexposed males, no effects on female fertility (mating and reproductive performance) were observed at any of the concentrations tested (up to 7050 mg/m^3) (OECD 2008).

One developmental toxicity study was available for *n*-propyl alcohol. In this study, pregnant female rats were exposed at concentrations of 0, 3500, 7000 or 10 000 ppm (0, 8610, 17 200 or 24 600 mg/m^3, respectively) for 7 hours/day from gestation day (GD) 1 to 19. The NOAEC for maternal and developmental toxicity was 3500 ppm (8610 mg/m^3) on the basis of reduction of food intake in dams exposed to the two highest concentrations and decrease in maternal body weight gain at 10 000 ppm and increased pre- and post-implantation losses (resulting in increased resorptions and decreased live pups per litter), decreased fetal body weights and a dose-related increase in the incidence of skeletal, visceral and external malformations in rats exposed to 10 000 ppm and 7000 ppm (24 600 mg/m^3 and 17 200 mg/m^3, respectively) *n*-propyl alcohol (OECD 2008).

For *n*-butyl acetate, inhalation developmental toxicity studies have been conducted in rats and rabbits. In both studies, animals were exposed to *n*-butyl acetate for varying intervals during pregnancy. Both studies resulted in LOAECs for developmental toxicity of 1500 ppm (7.05 mg/L or 7050 mg/m^3) on the basis of maternal toxicity (decrease in food consumption and body weight gains) and increases in skeletal variations or anomalies, but no increase in fetal malformations, at the only dose tested (OECD 2008).

Genotoxicity

On the basis of the available data for propyl acetate (negative result in a bacterial mutation assay) and its metabolite and analogues (negative result for *n*-propyl alcohol and ethyl acetate in *in vitro* SCE assays and in an *in vitro* micronucleus test and negative results for ethyl acetate and *n*-butyl acetate in *in vitro* chromosomal aberrations assays), the OECD concluded that it is unlikely that this substance induces genotoxic effects *in vivo* (OECD 2008).

Carcinogenicity

There are no carcinogenicity studies for propyl acetate. No studies were available for *n*-propyl alcohol or the structural analogues *n*-butyl acetate and ethyl acetate (OECD 2008). In its assessment of acetate esters, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) concluded that, on the basis of the limited available information, substances in this group, such as propyl acetate, are not likely to be human carcinogens (AGDH 2014).

Characterization of risk

The OECD (2008) review was used to inform the health effects characterization of propyl acetate. The OECD (2008) considered the data on ethyl acetate and *n*-butyl acetate, two structural analogues of propyl acetate, as well as the information on *n*-propyl alcohol, formed through hydrolysis of propyl acetate once absorbed.

Inhalation is a primary route of exposure to propyl acetate for the general population in Canada as a result of intermittent use of products available to consumers (e.g., nail products, aerosol paint products, adhesives). Oral exposure to propyl acetate may occur through the diet as a result of its potential use as a food flavouring agent. However, a JECFA evaluation of this use concluded that the substance posed “no safety concern” based on current levels of intake (WHO 1998).

The main reported health effects of ethyl acetate and *n*-butyl acetate following inhalation exposure were site-of-contact effects, generally at high concentrations. According to the OECD (2008), similar site-of-contact effects on the nasal epithelium are expected in response to repeated inhalation exposure to *n*-propyl acetate. Decreases in food consumption and body weight gain were also noted in repeated-dose studies, but no adverse effect of systemic toxicity was seen. Propyl acetate is unlikely to have genotoxic or carcinogenic potential. Changes in male fertility and developmental toxicity (fetal malformations and/or variations) were observed following exposure to *n*-propyl alcohol and the analogue *n*-butyl acetate. However, the changes in male fertility were reversible, the developmental effects were noted in presence of maternal toxicity (decrease food consumption and decrease in maternal body weight gain), and these effects were observed only at very high, excessive concentrations (male fertility at 17 200 mg/m^3 for *n*-propyl alcohol and developmental toxicity at 7050 mg/m^3 (skeletal variations only) and 17 200 mg/m^3 for *n*-butyl acetate and *n*-propyl alcohol, respectively). For the purposes of this screening assessment, propyl acetate is therefore considered to be of low hazard potential.

As propyl acetate is considered to be of low hazard potential, derivation of exposure estimates was not considered to be warranted, and the risk to human health is considered to be low.

7.1.4 Isobutyl acetate

Exposure assessment

As isobutyl acetate is considered to be of low hazard potential (see health effects assessment below), quantitative estimates of exposure to the general population were not derived. This section provides general information on exposure to isobutyl acetate.

Ambient air concentrations for isobutyl acetate were measured in four Canadian studies in Windsor, Regina, Halifax and Edmonton (Health Canada 2010a, b, 2012, 2013). Geometric mean ambient air concentrations were below the MDL, with maximum values ranging from below the MDL to 4.9 µg/m^3 (Health Canada 2010a, b, 2012, 2013). The detection frequency ranged from 0% to 17%.

Indoor air concentrations for isobutyl acetate were also measured across the same four Canadian studies referred to above. Geometric mean concentrations ranged from below the MDL to 0.15 µg/m^3, with maximum values ranging from below the MDL to 58.0 µg/m^3 (Health Canada 2010a, 2010b, 2012, 2013). Summary data for isobutyl acetate measured in indoor air in homes in Quebec City using passive sampling between November 2008 and March 2010 were also available (Won and Lusztyk 2011). Isobutyl acetate was detected in 64% of the samples. The geometric mean and maximum reported concentrations of isobutyl acetate in indoor air were 0.27 µg/m^3 and 3.0 µg/m^3, respectively.

Measured concentrations of isobutyl acetate in water or dust were not identified in Canada.

Isobutyl acetate has been evaluated as a flavouring substance by JECFA, which concluded that the substance posed “no safety concern” based on current levels of intake when used as a flavouring agent (WHO 1998). There is no definitive information available concerning the potential use of isobutyl acetate as a food flavouring agent in Canada, but its use, if any, as a food flavouring agent may result in oral exposure to the general population of Canada. Isobutyl acetate may be used as a component in the manufacture of food packaging materials with no direct food contact, and therefore dietary exposure is not expected (personal communication, email from RMB, HC, to ESRAB, HC, dated August 17, 2015; unreferenced).

Isobutyl acetate was identified in cosmetic products available to consumers in Canada, primarily nail products (personal communication, emails from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Use of these products may result in inhalation exposure to the substance.

Isobutyl acetate is found in a range of products available to consumers in Canada, including primers, putties, lacquers and aerosol paints (SDS 2014d, 2018d, 2018e). Use of these products may result in inhalation and dermal exposure to the general population in Canada.

Health effects assessment

Isobutyl acetate has been reviewed by the OECD (2003a), and this review informed the health effects characterization in this assessment. A literature search was conducted from the year prior to the OECD SIAR (January 2002) to December 2020. No additional health effects studies were identified.

Isobutyl acetate was considered by the OECD to cause skin, eye and respiratory tract irritation, as well as transient effects that may become evident only at high exposure levels. The OECD classified this substance as low priority for further work (OECD 2003a).

Exposure to isobutyl acetate via dermal, inhalation, and oral administration results in the rapid appearance of isobutanol (CAS RN 78-83-1) in the systemic circulation due to complete hydrolysis of the substance by esterase enzymes present in the skin, lungs, and gastrointestinal tract. Since exposure to isobutyl acetate results in systemic exposure to isobutanol, data for this substance were taken into consideration by the OECD for the assessment of the systemic toxicity of isobutyl acetate (OECD 2003a).

Repeated-dose toxicity

No repeated-dose toxicity studies for isobutyl acetate were identified. Two isobutanol studies were considered to be key studies by the OECD. It was concluded that "repeated exposures to moderate to high concentrations of isobutanol by the inhalation and oral routes of exposure are well tolerated in rats" (OECD 2003a).

A subchronic (90-day) study was conducted on rats via inhalation at concentrations of 0, 758, 3030, and 7575 mg/m^3 (0, 250, 1000, and 2500 ppm, respectively) isobutanol. The critical effect level identified by the OECD was a NOAEC of 3030 mg/m^3 based on very slight increases (9%) in red blood cell parameters (erythrocyte count, hemoglobin, and hematocrit measures) in female rats exposed to 7575 mg/m^3. The OECD noted that these slight changes were of questionable biological significance. No evidence of neurotoxicological effects were observed at any of the concentrations tested (up to 7575 mg/m^3) (OECD 2003a).

In a subchronic (13-week), gavage study conducted on rats (30/sex/group) exposed to isobutanol at doses of 0, 100, 316, and 1000 mg/kg bw/day, the critical effect level and corresponding hazard endpoint identified by the OECD was a NOAEL of 316 mg/kg bw/day, on the basis of hypoactivity and ataxia noted at the next dose level (1000 mg/kg bw/day), effects that were resolved after four weeks of recovery (OECD 2003a).

Reproductive/developmental toxicity

No reproductive and/or developmental toxicity studies were available for isobutyl acetate.

A two-generation inhalation reproductive toxicity study conducted in rats with isobutanol identified a critical effect level (NOAEC) of 7575 mg/m^3 on the basis of no parental systemic, reproductive, or neonatal toxicity at the highest dose tested (OECD 2003a).

In two developmental toxicity studies, rats and rabbits were exposed via inhalation at concentrations of 0, 0.5, 2.5 or 10 mg/L (0, 500, 2500, and 10 000 mg/m^3) isobutanol for 6 hours/day from GD 6 to GD 15 in rats and from GD 7 to GD 19 in rabbits. No developmental effects or fetotoxicity effects were observed at any of the concentrations tested in either species in either study (OECD 2003a).

Genotoxicity

Isobutyl acetate was not mutagenic in an Ames test using *Salmonella typhimurium*, indicating that this substance is not a genotoxicant (OECD 2003a). Furthermore, isobutanol was negative in an *in vivo* mouse micronucleus study in which isobutanol was administered once orally to male and female NMRI mice at doses up to 2000 mg/kg body weight (OECD 2003a).

Carcinogenicity

There are no carcinogenicity studies for isobutyl acetate. In its assessment of acetate esters, NICNAS (2014) concluded that, on the basis of the limited available information, substances in this group (such as isobutyl acetate) are not likely to be human carcinogens (AGDH 2014).

Characterization of risk

The OECD (2003a) review informed the health effects characterization of isobutyl acetate. Exposure to isobutyl acetate via the dermal, inhalation and oral routes results in the rapid appearance of isobutanol in the systemic circulation, and available information for isobutanol was considered by the OECD in its assessment of isobutyl acetate (OECD 2003a).

Exposure of the general population in Canada to isobutyl acetate is expected to occur primarily via inhalation from its presence in products available to consumers, including nail polishes, putties, primers and aerosol paints and from its presence in indoor or ambient air. Oral exposure may occur through the diet as a result of its potential use as a food flavouring agent.

No adverse systemic effects were observed in available studies for isobutanol (at doses up to 1000 mg/kg bw/day following subchronic oral exposure and at concentrations up to 7575 mg/m^3, the highest concentration tested, following subchronic inhalation exposure). In reproductive and developmental toxicity studies conducted with isobutanol, no parental, reproductive, or neonatal adverse effects were reported in animals exposed via inhalation to concentrations up to 10 000 mg/m^3. Isobutyl acetate is unlikely to have genotoxic or carcinogenic potential.

No adverse effects on the central or peripheral nervous system were observed in rats following subchronic oral and inhalation exposure to isobutanol. Only slight and transient effects were observed in exposed animals, such as reduction in response to an external stimulus in rats exposed via inhalation and hypoactivity and ataxia in rats exposed via gavage to 1000 mg/kg bw/day isobutanol for 13 weeks.

The OECD classified this substance as low priority for further work (OECD 2003a).

Considering the available health effects information for isobutanol, isobutyl acetate is considered to be of low hazard potential.

As isobutyl acetate is considered to be of low hazard potential, characterization of exposure potential (i.e., derivation of exposure estimates) was not warranted. The risk to human health is considered to be low.

7.1.5 Methyl dodecanoate

Exposure assessment

As methyl dodecanoate is considered to be of low hazard potential (see Health effects assessment below), quantitative estimates of exposure of the general population were not derived. This section provides general information on exposure to methyl dodecanoate.

Methyl dodecanoate is associated with a moderate volatility and low water solubility. Exposure of the general population to methyl dodecanoate may occur via the inhalation, oral or dermal route.

Won and Lusztyk (2011) monitored indoor air concentrations of methyl dodecanoate in homes in Quebec City between November 2008 and March 2010 using passive sampling and reported its detection in 6% of the samples. The geometric mean and maximum reported concentrations of methyl dodecanoate in indoor air were 0.63 $\mu g/m^3$ and 1.01 $\mu g/m^3$, respectively. Methyl dodecanoate was also identified in household dust collected from 50 dust samples from homes in Quebec City (Won and Lusztyk 2011). The geometric mean concentration of methyl dodecanoate in dust samples was reported to be 0.87 µg/g dust (detection frequency of 10%) with a maximum value of 18.7 µg/g dust.

Methyl dodecanoate has been evaluated as a flavouring substance by JECFA, which concluded that the substance posed “no safety concern” based on current levels of intake when used as a flavouring agent (WHO 1998). There is no definitive information available concerning the potential use of methyl dodecanoate as a food flavouring agent in Canada; however, its use, if any, as a food flavouring agent may result in oral exposure to the general population of Canada.

Methyl dodecanoate is found as a non-medicinal ingredient in a dermally applied prescription and/or non-prescription drug, and use of this product may result in dermal exposure to the general population in Canada. Methyl dodecanoate is also found in face moisturizers used as cosmetics.

Health effects assessment

OECD (2013) summarized the health effects literature for methyl dodecanoate. This assessment informed the health effects characterization in this screening assessment.

A literature search was conducted from the year prior to the OECD SIAR (January 2012) to December 2020. No additional health effects studies were identified.

Methyl dodecanoate was considered by the OECD to have a “low hazard profile” based on the available dataset. There were no treatment-related adverse effects observed in rats in a combined oral repeated-dose and reproductive/developmental toxicity screening test up to and including the limit dose of 1000 mg/kg bw/day. Also, methyl dodecanoate was considered non-genotoxic *in vitro*. No data were available on the carcinogenicity of this substance.

The OECD did not identify effects of concern for human health and classified this substance as low priority for further work. Methyl dodecanoate is therefore considered to be of low hazard potential.

Characterization of risk

As methyl dodecanoate is considered to be of low hazard potential, characterization of exposure potential (i.e., derivation of exposure estimates) was not considered to be warranted, and the risk to human health is considered to be low.

7.1.6 Methyl butanoate

Exposure assessment

Methyl butanoate was measured in only 4% of indoor air samples in homes in Quebec City between November 2008 and March 2010, with a maximum reported concentration of 0.18 μg/m^3 (Won and Lusztyk 2011).

Measured concentrations of methyl butanoate in ambient air, water soil or dust were not identified in Canada. This substance was not reported to be imported or manufactured above reporting thresholds in Canada, and therefore releases from industrial sources are not expected.

Methyl butanoate has been evaluated as a flavouring substance by JECFA, which concluded that the substance posed “no safety concern” based on current levels of intake when used as a flavouring agent (WHO 1998). In the absence of data on actual use, if any, in Canada, the per-capita intake estimate for the US population derived by JECFA of 44 µg/person/day (0.73 μg/kg bw/day based on the average body weight of 60 kg for the general population) is an acceptable estimate of possible Canadian dietary exposure to methyl butanoate from its potential use as a food flavouring agent for the general population (1 year of age and older) (WHO 1998; personal communication, email from FD, HC, to ESRAB, HC, dated March 15, 2021; unreferenced).

Health effects assessment

A literature search was conducted up to December 2020. No health effects studies were identified.

Following absorption, it is expected that methyl butanoate undergoes rapid hydrolysis by non-specific esterases present in the blood and tissues to form *n*-butyric acid (CAS RN 107-92-6) and methanol (CAS RN 67-56-1). Available information on the two metabolites was examined to inform the human health assessment of methyl butanoate. Both *n*-butyric acid and methanol were reviewed under the CMP; *n*-butyric acid was reviewed as part of the screening assessment of the Carboxylic Acids Group (ECCC, HC 2019) and methanol was reviewed as part of the draft screening assessment of the Alcohols Group (ECCC, HC 2022).

Methyl butanoate is also structurally similar to another ester in this grouping, methyl dodecanoate (CAS RN 111-82-0). Available information on this substance was also considered in this assessment.

n-Butyric acid

Repeated-dose toxicity

n-Butyric acid was reviewed by the OECD (2003), and this review was used to inform the health effects characterization of this substance in the screening assessment of the Carboxylic Acids Group (ECCC, HC 2019).

The screening assessment of the Carboxylic Acids Group concluded that, on the basis of available information on the precursors of *n*-butyric acid (*n*-butanol and *n*-butyl acetate), *n*-butyric acid was not predicted to have carcinogenic or genotoxic potential and is not expected to cause reproductive and developmental effects. Systemic effects (e.g., increased testes weights and increased adrenal weights) were observed in experimental animals following repeated inhalation exposure to *n*-butyric acid for 13 weeks, but only at high doses (e.g., as high as 7128 or 14 256 mg/m^3), doses that are considered irrelevant to potential human exposure levels. In addition, only transient effects were observed at the highest dose tested in a repeated-dose oral study. *n*-Butyric acid was therefore considered to be of low hazard potential.

Methanol

Methanol was reviewed in the draft screening assessment for the Alcohols Group under the CMP (ECCC, HC 2022), and information is summarized in section 7.1.1 (Health Effects Assessment) of this document. Using a similar approach as that used for methyl acetate and methyl hexanoate for methyl butanoate (i.e., being immediately degraded to methanol at a molar ratio of 1), the methanol reference values were adjusted to reflect exposure to methyl butanoate to derive values of 6.4 mg/kg bw/day and 64 mg/m^3.

Methyl dodecanoate

The assessment of this substance is presented in section 7.1.5. Methyl dodecanoate was considered by the OECD (2013) to have a “low hazard profile” based on the available dataset. There were no treatment-related adverse effects observed in a combined oral repeated-dose and reproductive/developmental toxicity screening test up to and including the limit dose of 1000 mg/kg bw/day. Also, methyl dodecanoate was considered non-genotoxic *in vitro*. The OECD classified this substance as low priority for further work.

Characterization of risk

Following absorption, it is expected that methyl butanoate undergoes hydrolysis to form *n*-butyric acid and methanol.

Both *n*-butyric acid and methanol have been assessed under the CMP (ECCC, HC 2019; ECCC, HC 2022). In the CMP assessment, *n*-butyric acid was considered to be of low hazard potential, and risk to human health from exposure to this substance was also considered to be low. No genotoxic or carcinogenic potential has been observed for methanol. Potential developmental effects associated with methanol are considered in this assessment. The RfC and RfD derived by the US EPA for inhalation and oral exposure to methanol (20 mg/m^3 and 2 mg/kg bw/day, respectively) were adjusted to reflect exposure to methyl butanoate, resulting in values of 64 mg/m^3 and 6.4 mg/kg bw/day, respectively (assuming methyl butanoate is immediately degraded to methanol at a molar ratio of 1:1). The reported maximum air concentration (0.18 μg/m^3) and intake (0.73 μg/kg bw/day) for methyl butanoate are well below the adjusted methanol inhalation and oral reference values.

Methyl butanoate is also structurally similar to another ester of subgroup A, methyl dodecanoate. Methyl dodecanoate was considered by the OECD (2013) to have a “low hazard profile.”

Considering the available information for the metabolites and the analogue methyl dodecanoate, the risk to human health from exposure to methyl butanoate is considered low.

7.1.7 Dimethyl glutarate

Exposure assessment

As dimethyl glutarate is considered to be of low hazard potential (see Health effects assessment below), quantitative estimates of exposure to the general population were not derived. This section provides general information on exposure to dimethyl glutarate.

Dimethyl glutarate is a liquid with a moderate vapour pressure and very high water solubility. No empirical data were found for dimethyl glutarate in ambient air, water or soil in Canada. However, it was identified to be present in household dust collected from 50 dust samples from homes in Quebec City (Won and Lusztyk 2011). The geometric mean concentration of dimethyl glutarate in dust samples was reported to be 0.34 µg/g dust (detection frequency of 32%) with a maximum value of 7.8 µg/g dust.

Dimethyl glutarate may be used as a component in an incidental additive (hand sanitizer) used in food processing establishments in Canada with no potential for direct food contact. Therefore, dietary exposure is not expected (personal communication, email from FD, HC, to ESRAB, HC, dated December 5, 2016; unreferenced).

This substance is found in adhesives, cleansers, and nail polish remover products in Canada (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Use of these products may result in dermal or inhalation exposure to the general population in Canada.

Dimethyl glutarate is used in a variety of products available to consumers that may result in dermal or inhalation exposure to the general population in Canada, including premoistened towels or hand wipes, paint/varnish removers, sealants as part of countertop refurbishing kits, graffiti removers and air freshening products (SDS [date unknown], 2013b, 2015e; Household Products Database 1993-).

In past surveys performed in Denmark, dimethyl glutarate was detected at low levels in some products (e.g., toothbrushes, wooden children's toys, and sex toys (Svendsen et al. 2004; Nilsson et al. 2006; Hansen and Pedersen 2005). These surveys did not identify dimethyl glutarate as a substance for further analysis or prioritization.

Health effects assessment

Only limited health effects information was identified for dimethyl glutarate. However, available data were identified from a mixture, dibasic esters (DBE; CAS RN 95481-62-2). DBE mainly contains dimethyl glutarate (55% to 75%) and two other structurally similar constituents, dimethyl adipate (15% to 27%; CAS RN 627-93-0) and dimethyl succinate (10% to 25%; CAS RN 106-65-0) (US EPA 2014). The data from this mixture have been considered and were used to inform this human health assessment.

Repeated-dose toxicity

In a repeated-dose oral (gavage) study, DBE did not result in systemic toxicity to rats dosed daily for 1 month up to 1000 mg/kg bw/day, the highest dose tested (HPVIS 2017).

With respect to the dermal route, no treatment-related effects were observed when rats (10/sex/dose) were exposed up to 1000 mg/kg bw/day DBE, for 6 hours/day, 7 days/week, for 2 weeks (Anonymous 2000, as cited in ECHA c2007-2017e).

A subchronic inhalation (whole-body) study was conducted with dimethyl glutarate in rats. Test animals (36/sex/dose) were exposed to 0, 10, 50 and 400 mg/m^3 for 6 hours/day, 5 days/week, for 90 days. The NOAEC was 50 mg/m^3. In groups exposed to 400 mg/m^3, decrease in body weight gain was noted in males and decreased food consumption and degeneration/atrophy of the olfactory mucosa was observed in both sexes. There were also hormonal changes (e.g., decreased serum testosterone and serum luteinizing hormone (LH) concentrations), but these effects were considered by the authors to not be of toxicological significance as the decrease in hormone levels did not result in a reduction of epididymal sperm count (HPVIS 2017; Anonymous 2000, as cited in ECHA c2007-2017f).

Another subchronic inhalation (whole-body) study was conducted in rats (10/sex/dose) exposed for 6 hours/day, 5 days/week, for 14 weeks, to 0, 160, 400 and 1000 mg/m^3 of the mixture DBE. Dose-related degenerative effects on the olfactory epithelium were observed at all dose levels; however, pathological examination of all other tissues, excluding nasal olfactory epithelium, demonstrated no effects from DBE exposure to concentrations up to 1000 mg/m^3. Decreased relative liver weights were reported in all exposed groups. However, according to the authors of the study, the biological significance of the liver effects is not known due to the absence of a recovery period and the lack of histopathological findings in the liver (HPVIS 2017; Anonymous 1987, as cited in ECHA c2007-2017g).

In another inhalation (whole-body) study, rats were exposed for up to 13 weeks to DBE. Test animals (40/sex/dose total) were exposed 6 hours/day, 5 days/week, to 0, 20, 76 and 390 mg/m^3. After 13 weeks, degeneration of the olfactory epithelium was present at all DBE concentrations in female rats but only at the mid and high concentrations in male rats, resulting in a LOAEC for females and NOAEC for males of 20 mg/m^3. At the end of the 6-week recovery period, histological changes associated with repair of the olfactory mucosa were noted. Liver weights of females exposed to 390 mg/m^3 were decreased compared to controls, but this effect was not observed at the end of the recovery period. A slight decrease in serum sodium concentration was observed after 13 weeks in all rats exposed at the two highest doses, which mostly resolved during the recovery period (Keenan et al. 1990; Anonymous 1987, as cited in ECHA c2007-2017h).

The US EPA (2014) suggested that the degeneration of olfactory mucosa was related to the hydrolysis of dimethyl glutarate by carboxylesterases located in the nasal/olfactory epithelium due to a dicarboxylic acid metabolite. According to the US EPA, these local effects are expected to be of much lower impact in humans because of major anatomical and physiological differences between rats and humans. Rats have a larger surface of nasal epithelium, different air flow and breathing pattern (rats are obligate nose breathers), and greater carboxylesterase activity in nasal/olfactory epithelium than humans. *In vitro* studies with human nasal tissue homogenates suggest that metabolism of the mixture DBE in human nasal tissue is 100 to 1000 times less active than in rat nasal tissue. Given the absence of systemic toxicity and the expectation that humans would be much less sensitive to olfactory responses than rodents, the US EPA concluded that the local effects were not sufficiently adverse to be used as an endpoint for risk assessment (US EPA 2014).

Reproductive/developmental toxicity

In reproductive/developmental toxicity studies conducted with dimethyl glutarate and DBE, no reproductive and developmental effects were noted. The only effects observed following inhalation exposure to those substances were site-of-contact effects (degeneration of olfactory mucosa) and decrease in food consumption and body weight gain in parental animals.

A one-generation study was conducted in rats for DBE via the inhalation route. Test animals (20/sex/dose) were exposed to 0, 160, 400 and 1000 mg/m^3 for 6 hours/day, 5 days/week, for 14 weeks prior to mating. No effect on mating performance, fertility, length of gestation, or progeny numbers, structure and viability was noted. However, a statistically significant decrease in pup weights was noted at birth and during weaning in the 1000 mg/m^3 group in presence of parental toxicity. The NOAEC for parental toxicity was 160 mg/m^3 on the basis of decreased body weight and a decrease in relative liver weight and presence of mild to moderate olfactory epithelium squamous metaplasia in both sexes at higher concentrations (Anonymous 1988 and 1998, as cited in ECHA c2007-2017i; Kelly et al. 1998).

A developmental study was conducted in rabbits with dimethyl glutarate via the inhalation route. Test animals (22 females/dose) were exposed (whole body) to 0, 30, 100, 300 and 1000 mg/m^3, 6 hours/day from GD 7 to GD 28. The NOAEC for developmental toxicity was 1000 mg/m^3, on the basis of no developmental effects observed. The NOAEC for maternal toxicity was 100 mg/m^3, on the basis of decrease in body weight gain from 300 mg/m^3. Food consumption was also significantly decreased at 1000 mg/m^3 (Anonymous 2003, as cited in ECHA c2007-2017j).

A developmental study was also conducted in rats with DBE via the inhalation (whole-body) route. Test animals (20-24 females/dose) were exposed to 0, 160, 400 and 1000 mg/m^3, 6 hours/day from GD 7 to GD 16. Dams were sacrificed on GD 21. The NOAEC for developmental toxicity was 1000 mg/m^3, on the basis of no developmental effects observed. The NOAEC for maternal toxicity was 160 mg/m^3, the lowest concentration tested, on the basis of a significant decrease in maternal body weight and food consumption at 400 mg/m^3 and an increase in perinasal staining and wet fur (significant at the highest concentration) (Alvarez et al. 1995; Anonymous 1995, as cited in ECHA c2007-2017k).

Genotoxicity

Dimethyl glutarate was negative in bacterial mutation assays using *Salmonella typhimurium* strains TA97, TA98, TA100, and TA1535, with and without metabolic activation (NTP 2016). Dimethyl glutarate did not demonstrate mutagenic potential in the *in vitro* HPRT (hypoxanthine-guanine phosphoribosyl transferase) cell mutation assay using Chinese hamster ovary cells, with and without metabolic activation (Anonymous 2002, as cited in ECHA c2007-2017l). Negative results were also reported for DBE in an *in vitro* mammalian chromosomal aberration assay conducted with human peripheral blood lymphocytes, with and without metabolic activation (HPVIS 2017).

In *in vivo* assays, dimethyl glutarate did not cause chromosomal damage or bone marrow cell toxicity in rats (5/sex/dose) exposed to up to 2000 mg/m^3 via inhalation (whole-body) 6 hours/day for 2 days (Anonymous 2001, as cited in ECHA c2007-2017m; Huntingdon Life Sciences, Ltd 2001, as cited in HPVIS 2017).

Carcinogenicity

There are no data on the carcinogenic potential of dimethyl glutarate and the mixture DBE. However, the US EPA concluded that dimethyl glutarate did not show special alerts and was not expected to be carcinogenic in humans (US EPA 2014).

Characterization of risk

Only limited health effects information was identified for dimethyl glutarate. Available data have been identified from the mixture DBE, which is composed mainly of dimethyl glutarate and two other structurally similar components, dimethyl adipate and dimethyl succinate.

In repeated-dose oral and dermal studies (short-term to subchronic durations), no effects were observed in animals administered doses up to 1000 mg/kg bw/day. In inhalation studies, the only effects noted were reversible, such as decrease in food consumption and body weight gain, as well as site-of-contact effects (degeneration of olfactory mucosa). These site-of-contact effects could be considered transient based on evidence of repair of the mucosa 6 weeks post exposure (Keenan et al. 1990; Anonymous 1987, as cited in ECHA c2007-2017h) and may not be relevant to humans given differences in sensitivity to olfactory responses between humans and rats (US EPA 2014). While decreases in relative liver weight were noted in rats in a subchronic and a one-generation study with DBE, these decreases were not associated with histopathological findings in the liver and were transient and reversible. No reproductive or developmental effects were noted in animals exposed to concentrations up to 1000 mg/m^3. The US EPA concluded that dimethyl glutarate does not show special alerts and is not expected to be carcinogenic in humans (US EPA 2014). No evidence for genotoxicity was observed in the available empirical data for either substance.

Considering the available data for dimethyl glutarate and the mixture DBE, dimethyl glutarate is considered to be of low hazard potential, and therefore characterization of exposure potential (i.e., derivation of exposure estimates) was not considered to be warranted. The risk to human health is considered to be low.

7.1.8 Tetradecyl tetradecanoate

Exposure assessment

As tetradecyl tetradecanoate is considered to be of low hazard potential (see Health effects assessment below), quantitative estimates of exposure to the general population were not derived. This section provides general information on exposure to tetradecyl tetradecanoate.

Tetradecyl tetradecanoate is a solid with negligible vapour pressure and very low water solubility. No empirical data were found for tetradecyl tetradecanoate in air (indoor or ambient), water, dust or soil in Canada.

Tetradecyl tetradecanoate may be used as a component in an incidental additive (hand cleaner) used in food processing establishments with no potential for direct food contact, and therefore dietary exposure is not expected (personal communication, email from FD, HC, to ESRAB, HC, dated December 5, 2016; unreferenced).

In cosmetics, tetradecyl tetradecanoate is often identified as myristyl myristate. It is found in over 900 cosmetics in Canada, including antiperspirants/ deodorants, bath products, hair products, skin products, bleach, cleansers, fragrance products, massage products, nail polish, shampoo, shaving products, and sunless tanning products (email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Use of these products may result primarily in dermal exposure to the general population in Canada.

Tetradecyl tetradecanoate is found as a non-medicinal ingredient in topically applied natural health products and prescription and/or non-prescription drugs in Canada, including makeup, antiperspirants, moisturizers, sunscreens, and lip balms, with some products specifically for use on children. These products may result in dermal or oral exposure to the general population in Canada.

Health effects assessment

Limited health effects information was identified for tetradecyl tetradecanoate. After absorption, it is expected that tetradecyl tetradecanoate (also named tetradecyl myristate) undergoes rapid hydrolysis to a fatty acid (myristic acid; CAS RN 544-63-8) and long-chain alcohols (tetradecanol [CAS RN 112-72-1] and alcohols, C14-15 [CAS RN 75782-87-5]). Myristic acid has been reviewed by the OECD (2014) as part of the Aliphatic Acids Category assessment. Tetradecanol and C14-15 alcohol have also been reviewed by the OECD (2006) as part of its assessment of long-chain alcohols. These reviews were used to inform the health effects characterization of tetradecyl tetradecanoate. A literature search was conducted from the year prior to the publication of the OECD assessments up to December 2020, and no additional health effects studies which could result in points of departure lower than those identified by OECD (2006, 2014) were identified.

Hazard data from analogues were also used to inform the health effects assessment of tetradecyl tetradecanoate. Analogues were identified on the basis of structural similarity, similarity in physical-chemical properties, data availability, and the subgroupings used in Cosmetic Ingredient Review (CIR) reports (Becker et al. 2010; CIR 2013). These analogues include propylheptyl caprylate (CAS RN 868839-23-0), ethylhexyl laurate (CAS RN 20292-08-4), isodecyl laurate (CAS RN 94247-10-6), isopropyl myristate (CAS RN 110-27-0), isodecyl oleate (CAS RN 59231-34-4), tetradecyl oleate (CAS RN 22393-85-7), behenyl behenate (CAS RN 17671-27-1), and 2-ethylhexyl stearate (CAS RN 22047-49-0) (see section 2.1 and Appendix A for more information on the structures and physical-chemical properties, respectively). Literature searches were conducted up to June 2017 for these substances.

Toxicokinetics

No toxicokinetics data have been identified for tetradecyl tetradecanoate and its analogues. Only limited data have been identified for its expected metabolites, myristic acid, tetradecanol and alcohols, C14-15. Long (>12 carbon) chain aliphatic acids, such as myristic acid, are absorbed in the intestine and distributed in the blood as chylomicrons (OECD 2014). Aliphatic alcohols are efficiently eliminated and therefore not expected to have a tissue retention or bioaccumulation potential (Bevan 2001). Aliphatic alcohols are efficiently metabolized, and the biotransformation products are very similar or indistinguishable from those derived from common dietary sources (triglycerides).

Repeated-dose toxicity

There are no data available on the repeated-dose toxicity of tetradecyl tetradecanoate. Available data were identified via the oral route for its metabolites and analogues. However, no inhalation or dermal studies were identified.

In OECD (2014), repeated-dose oral (gavage or diet) exposure to aliphatic acids, including myristic acetate, a metabolite of tetradecyl tetradecanoate, did not result in systemic toxicity, with NOAELs greater than 1000 mg/kg bw/day. The OECD identified docosanoic acid (CAS RN 112-85-6) as the closest structural analogue with data to myristic acid. In a combined repeated-dose toxicity study with reproduction/developmental toxicity screening test, rats (13/sex/group) were administered docosanoic acid by oral gavage at doses of 0, 100, 300, and 1000 mg/kg bw/day. For males, the exposure period was 42 days; for females, the exposure period was from 14 days prior to mating to day 3 of lactation (minimum of 39 days of exposure). No deaths or changes in general condition, no changes in body weight gain or food consumption, and no adverse histopathological, hematological or biochemical effects were observed at any of the doses tested (OECD 2014).

Low systemic toxicity was expected for all routes following exposure for short-term and subchronic duration to tetradecanol/C14-15 alcohol, another metabolite of tetradecyl tetradecanoate. According to the OECD (2006), repeated exposure to aliphatic alcohols is generally without significant systemic toxicological findings, and the long-chain alcohols category is regarded to be of a low order of toxicity upon repeated exposure.

Information on the results of repeated-dose studies on the analogues of tetradecyl tetradecanoate was also collected.

In a subchronic, repeated-exposure study, rats were administered propylheptyl caprylate by gavage. Test animals (10/sex/dose) were exposed 7 days/week, for 90 days to 0, 100, 300 and 1000 mg/kg bw/day propylheptyl caprylate in soybean oil. No test article-related mortality was noted. No substance-related clinical signs of toxicity, changes in body weights, feed consumption, or estrous cycle, or effects on sperm were observed, and there were no effects on any clinical chemistry or hematology parameters. Animals exposed to the highest dose showed a statistically significant increase in the absolute and relative liver weights. No other macroscopic or microscopic changes in the organs were noted. The changes in the liver weights were considered to be a non-specific adaptive change to the high workload of the liver at the maximum dose (LPT 2006; AGDH 2008).

In a short-term oral study, rats of both sexes (number not given) were administered doses up to 4500 mg/kg bw/day of isodecyl laurate, 6 days/week, for 4 successive weeks. No treatment-related changes were observed at any dose level (AGDH 1998; CIR 2013).

A dose range-finding study was conducted with isodecyl oleate to determine the appropriate dose levels for a combined repeated-dose toxicity study and reproduction/developmental toxicity screening test. In the study, rats (5/sex/dose) were exposed by gavage to 100, 300 and 1000 mg/kg bw/day of isodecyl oleate, 7 days/week, for 14 days. There was no mortality during the study period. No treatment-related clinical signs were observed. The body weight, body weight gain and mean food consumption were comparable between the control group and treatment groups during the study period. No gross pathological changes were observed, including the appearance and size of the gonads, adrenal glands, uterus, and accessory reproductive organs (Anonymous 2012, as cited in ECHA c2007-2017n).

In the combined repeated-dose toxicity study, rats (10/sex/dose) were exposed by gavage to 100, 300 and 1000 mg/kg bw/day of isodecyl oleate, 7 days/week. In males, the daily administration of the test item was started 2 weeks before mating and lasted until test day 35, which was 1 day before sacrifice. In females, the daily administration of the test item was started 2 weeks before mating and continued up to at least day 3 of lactation (maximum 56 days of treatment). The NOAEL in females was 300 mg/kg bw/day, based on a statistically significant decrease (-9.7%) in body weight during lactation and a statistically significant reduction (-21.7%) in food consumption at the next dose of 1000 mg/kg bw/day. No effects were observed in males at any dose (Anonymous 2013, as cited in ECHA c2007-2017o).

In a dose-ranging study, rats (3/sex/dose) were exposed by gavage to 100, 300, and 1000 mg/kg bw/day of tetradecyl oleate, 7 days/week, for 2 weeks. Minor changes were observed in organ weights, including decreases in the absolute and relative thymus weight (approximately -18%) in males receiving 1000 mg/kg/day and statistically significant decreases in absolute and relative kidneys weight (-12%, for absolute weights) in females receiving 1000 mg/kg/day. The NOAEL was determined to be greater than 1000 mg/kg bw/day in both males and females (Anonymous 2013, as cited in ECHA c2007-2017p).

In a combined repeated-dose toxicity study with reproduction/developmental toxicity screening test, rats (10/sex/dose) were exposed by gavage to 100, 300 and 1000 mg/kg bw/day of tetradecyl oleate, 7 days/week. In males, the daily administration of the test item was started 2 weeks before mating and lasted until test day 28 to 29, which was 1 day before sacrifice. In females, the daily administration of the test item was started 2 weeks before mating and continued until day 3 post-partum (maximum of 54 days of treatment). Statistically significant fluctuations of some biochemical parameters (mean group values) were recorded, such as increased glucose in males dosed with 100 and 1000 mg/kg bw/day (48%), increased urea in those receiving 100 mg/kg bw/day (19%), increased aspartate aminotransferases in females dosed with 300 mg/kg bw/day (35%), and decreased bilirubin (81%) and increased potassium (10%) in those treated with the highest dose when compared to controls. Due to the lack of dose- and sex-consistency and to the absence of other relevant findings, the above alterations were considered unrelated to treatment, and the NOAEL was considered to be 1000 mg/kg bw/day (Anonymous 2014, as cited in ECHA c2007-2017q).

In a dose range-finding study, rats (3/sex/dose) were exposed by gavage to 100, 500 and 1000 mg/kg bw/day of behenyl behenate, 7 days/week, for 2 weeks. No adverse effects were reported at any dose (Anonymous 2012, as cited in ECHA c2007-2017r). In a combined repeated-dose toxicity study with reproduction/developmental toxicity screening test, rats (10/sex/dose) were administered behenyl behenate at doses of 100, 300, and 1000 mg/kg bw/day by gavage. Males were exposed 2 weeks prior to mating and at least up to and including the day before sacrifice (day 49 of treatment). Females were exposed 2 weeks prior to mating and at least up to and including the day before sacrifice (day 4 postpartum). No effects were observed at any dose in either sex (Anonymous 2014, as cited in ECHA c2007-2017s).

In a short-term study, rats (10/sex/dose) were administered 0, 100, 500 and 1000 mg/kg bw/day of isopropyl myristate by gavage, 5 days/week, for 28 days. No treatment-related changes were observed at any dose tested (Anonymous 1983, as cited in ECHA c2007-2017t).

Reproductive/developmental toxicity

There are no data available on the reproductive toxicity of tetradecyl tetradecanoate. A summary of the available data for the two expected metabolites is provided.

In a combined repeated-dose and reproductive/developmental toxicity test described earlier for docosanoic acid, no effects on reproduction or on developmental parameters were observed at any dose (up to 1000 mg/kg bw/day) (OECD 2014). Additionally, no effects on fertility or on reproductive organs and no developmental effects were observed in studies conducted with aliphatic acids. The OECD indicated that the weight of evidence supports the lack of reproductive and developmental toxicity potential of the aliphatic acids category (OECD 2014).

In the OECD report (2006), it is concluded that the long-chain alcohols category, which includes tetradecanol/alcohols, C14-15, is considered without a potential for adverse effects on fertility and reproductive toxicity. Similarly, developmental toxicity studies conducted with aliphatic alcohols have confirmed the lack of maternal toxicity and potential developmental effects of these substances.

Information on reproductive/developmental toxicity of analogues of tetradecyl tetradecanoate was also identified.

In the combined repeated-dose and reproductive/developmental toxicity test described earlier for isodecyl oleate (Anonymous 2013, as cited in ECHA c2007-2017o), the NOAEL for reproductive toxicity was determined to be 300 mg/kg bw/day on the basis of a statistically significant increase in post-implantation loss, a non-statistically significant decrease in birth index, and an increase in the number of stillbirths, leading to a statistically significant reduction in the live birth index at the highest dose tested. The NOAEL for parental toxicity was also 300 mg/kg bw/day, based on a slight reduction in body weight and food consumption in females at the highest dose. No effect in males was reported.

In the combined repeated-dose and reproductive/developmental toxicity tests described earlier for tetradecyl oleate and behenyl behenate (Anonymous 2014, as cited in ECHA c2007-2017q, Anonymous 2014, as cited in ECHA c2007-2017s), no systemic or reproductive effects were observed for either substance.

A developmental study was conducted in which female rats were administered doses of 0, 100, 300, and 1000 mg/kg bw/day of 2-ethylhexyl stearate, once daily from GD 6-15. Dams were sacrificed on GD 20. No developmental effects were observed (Anonymous 2000, as cited in ECHA c2007-2017u).

Overall, tetradecyl tetradecanoate is not considered to have potential for reproductive and developmental toxicity. No effects were expected for the two main metabolites. Furthermore, no developmental effects were noted with the analogue 2-ethylhexyl stearate. While reproductive effects were noted in a study conducted with isodecyl oleate, these effects were noted only at the limit dose (1000 mg/kg bw/day) and in presence of maternal toxicity. No equivalent reproductive or parental effects were noted in similar reproductive/developmental toxicity tests conducted with the two analogues tetradecyl oleate and behenyl behenate.

Genotoxicity

Tetradecyl tetradecanoate showed negative results in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with and without metabolic activation (Anonymous 2000, as cited in ECHA c2007-2017v).

The OECD (2014) identified docosanoic acid as the closest structural analogue with data to the metabolite myristic acid. Negative results were observed when *Salmonella* *typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* WP2 uvrA were exposed to docosanoic acid in the presence and absence of metabolic activation. According to OECD (2014), the weight of evidence indicates that members of the aliphatic acids category are not expected to be genotoxic.

Negative results were reported in an Ames test for alcohols, C14-15. According to the OECD (2006), the available data show a consistent lack of mutagenic activity across the whole range of linear alcohols, which include tetradecanol/alcohols, C14-15. Long-chain alcohols do not have genotoxic potential.

Information on the genotoxic potential of analogues of tetradecyl tetradecanoate was also identified.

Propylheptyl caprylate was negative in a bacterial mutation test using *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1573, with and without metabolic activation. It was not clastogenic to Chinese hamster V79 lung fibroblasts in an *in vitro* mammalian chromosomal aberration assay (AGDH 2008).

For isodecyl laurate, negative results were observed in a bacterial mutation test using *Salmonella typhimurium* strains TA98, TA100, and TA102 (AGDH 1998; CIR 2013).

For isopropyl myristate, negative results were observed in bacterial mutation tests using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with and without metabolic activation (Anonymous 1981, as cited in ECHA c2007-2017w; Anonymous 2014, as cited in ECHA c2007-2017x).

Carcinogenicity

There are no data on the carcinogenic potential of tetradecyl tetradecanoate and its analogues.

Limited data have been identified for the metabolite tetradecanol/alcohols, C14-15. According to OECD (2006), development of skin tumours was not reported for several members of the long-chain aliphatic alcohol category (such as 1-hexanol, 1-octanol, 1-decanol, 1-dodecanol, 1-tetradecanol, 1-hexadecanol, and 1-octadecanol) in mouse skin painting studies using repeated applications for periods of up to 60 to 70 weeks (Sicé 1966; Bingham 1969; Van Duuren 1976), indicating no evidence of a carcinogenic potential for this category. Long-chain aliphatic alcohols do not contain structural elements of concern for potential interaction with DNA and are non-mutagenic (OECD 2006).

Characterization of risk

After absorption, it is expected that tetradecyl tetradecanoate undergoes rapid hydrolysis to a fatty acid (myristic acid) and a long-chain alcohol (tetradecanol or alcohols, C14-15). Myristic acid has been reviewed by the OECD (2014) as part of the

Aliphatic Acids Category assessment. Repeated oral exposure to aliphatic acids in laboratory animals did not result in systemic adverse effects at doses up to 1000 mg/kg bw/day. Also, no effects on fertility or reproductive organs, and no developmental effects were observed in studies conducted on aliphatic acids. Members of the aliphatic acids category are not expected to be genotoxic.

Tetradecanol and alcohols, C14-15, have been reviewed by the OECD (2006) as part of the assessment of long-chain alcohols. According to the OECD (2006), the long-chain alcohols category is considered to be of a low order of toxicity upon repeated exposure. The substances included in this category are also considered to have a low potential for adverse effects on fertility, reproductive and developmental toxicity. Long-chain aliphatic alcohols do not contain structural elements of concern for potential interaction with DNA and are non-genotoxic.

Data from analogues (propylheptyl caprylate, ethylhexyl laurate, isodecyl laurate, isopropyl myristate, behenyl behenate, isopropyl myristate) were also considered. Short-term and subchronic repeated-dose studies as well as combined repeated-dose and reproductive/developmental toxicity tests were identified for the analogues. No systemic toxicity was seen in experimental animals after repeated-dose exposure to levels up to 1000 mg/kg bw/day for all these analogues. In addition, available information indicates that analogues are expected to lack reproductive and developmental toxicity potential. Based on the available information, the analogues are unlikely to have a genotoxic potential.

Considering the available health effects data for the metabolites and analogues, tetradecyl tetradecanoate is considered to be of low hazard potential, and therefore characterization of exposure potential (i.e., derivation of exposure estimates) was not considered to be warranted. The risk to human health is considered to be low.

7.1.9 2-Methoxypropyl acetate

Exposure assessment

Environmental media

No empirical data were identified for 2-methoxypropyl acetate in air, water or soil in Canada or elsewhere. 2-Methoxypropyl acetate is a liquid with a high vapour pressure and very high water solubility. Considering its physical and chemical properties, 2-methoxypropyl acetate may be present in air and water.

2-Methoxypropyl acetate is a potential impurity in 1-methoxy-2-propanol acetate (also known as propylene glycol monomethyl ether acetate, PGMEA or PMA) and has been reported to be present in the range of 0.3% to 0.5% (OECD 2003b). PMA has been reported to the National Pollutant Release Inventory since 2005, with reported releases in the range of 400 tonnes annually (primarily to air) (NPRI 2017). According to the NPRI, PMA is reported to be released to air by 71 facilities in Canada (ECCC 2019).

The US EPA SCREEN3 modelling tool (SCREEN3 2011) was used to estimate ambient air concentrations of PMA in Canada based on NPRI reported releases in 2019 and facility information, assuming that 2-methoxypropyl acetate may be present in PMA as an impurity up to 0.5%. One facility released approximately 33 tonnes of PMA to air in 2019 (ECCC 2019). At a 300-m distance (representing the distance from the source facility to residential areas), the daily (24-hour) air concentration of 2-methoxypropyl acetate was 4.61×10^{-3} mg/m3. Details on the SCREEN3 model and parameters used to derive this concentration are found in Appendix E

Concentrations of 2-methoxypropyl acetate in indoor air, drinking water and soil in Canada were estimated on the basis of its presence as a potential impurity in PMA and using the level III fugacity model known as ChemCAN (ChemCAN 2003). The total volume of use of PMA in Canada was not available, and therefore an upper bounding value of 100 000 tonnes (100 000 000 kg) of PMA in Canada was assumed. This volume of PMA was considered to be upper bounding for Canada as it was the reported value to be manufactured and/or imported into the European Economic Area (ECHA 2007-2017y). Assuming 2-methoxypropyl acetate may be present in PMA at up to 0.5%, 500 000 kg was considered to be an upper bound estimate of the total volume of 2-methoxypropyl acetate in use in Canada. The modelled concentrations for 2-methoxypropyl acetate derived from this approach were used to estimate exposure of the general population of Canada (see Table B-2, Appendix B).

General population exposure to 2-methoxypropyl acetate from environmental media ranged up to 0.44 μg/kg bw/day for 1-year-olds (see Table B-2, Appendix B).

Food

2-Methoxypropyl acetate may be used as a component in the manufacture of food packaging materials with no direct food contact, and therefore dietary exposure is not expected (personal communication, email from FD, HC, to ESRAB, HC, dated December 5, 2016, and March 15, 2021; unreferenced).

Products available to consumers

2-Methoxypropyl acetate (identified as 2-methoxypropyl-1-acetate) is on the list of ingredients that are described as prohibited for use in cosmetics in Canada (Health Canada [modified 2015]). In cosmetics, PMA (or methoxyisopropyl acetate) is on the list of ingredients that are described as restricted for use in cosmetics in Canada, with a maximum permitted concentration of 0.5% total of 2-methoxypropanol and/or 2-methoxypropyl-1-acetate (Health Canada [modified 2015]). Worst-case inhalation exposure estimates were derived assuming nail polish products contain 2-methoxypropyl acetate concentrations at less than 0.05% (assuming nail polish contains 10% PMA). The mean event concentration (i.e., during application) is estimated to be 0.12 mg/m^3, and the 6-hour time-weighted average air concentration is estimated to be 0.012 mg/m^3.

2-Methoxypropyl acetate has been noted in one product (an automotive scratch repair pen) (SDS 2017b). Exposure associated with this product is expected to be minimal. PMA, a potential source of 2-methoxypropyl acetate, is used in household products such as cleaners, paints, lacquers, and varnishes. In Canada, PMA has been identified in a range of products available to consumers, including aerosol paints and varnishes (SDS 2018f), automotive products such as spot putties (SDS 2020), scratch repair kits (SDS 2017b), rim dust blockers (SDS 2014e), and sealing products (SDS 2017c). Typical concentrations of PMA in products available to consumers is 5% to 15%, and occasionally as high as 20% (Dow 2015).

Although specific concentrations of 2-methoxypropyl acetate were not found in these products, inhalation exposure estimates were derived for sentinel products assuming a maximum concentration of 0.1% 2-methoxypropyl acetate (i.e., 20% PMA in products and PMA containing up to 0.5% 2-methoxypropyl acetate). Table 7-5 presents inhalation exposure estimates to 2-methoxypropyl acetate in products containing PMA. Although dermal exposure is expected to contribute to the overall exposure during use of products, given the high vapour pressure of 2-methoxypropyl acetate, the primary route of exposure is considered to be inhalation.

Table 7-5. Estimated exposures to 2-methoxypropyl acetate (based on concentrations of PMA) associated with the use of certain products

Product scenario	2-Methoxy-1-propyl acetate conc.	Mean event conc. (mg/m^3)	6-hour TWA conc. (mg/m^3)
Aerosol paint	0.1%	4.6	0.25
Putty/filler	0.1%	0.7	0.48

Abbreviations: conc., concentration; TWA, time-weighted average

Health effects assessment

2-Methoxypropyl acetate is classified as a reproductive toxicant (Repr 1B) on the harmonized classification and labelling table in Annex VI to the Classification, Labelling, and Packaging (CLP) Regulation (ECHA 2008).

2-Methoxypropyl acetate is rapidly hydrolyzed to 2-methoxypropanol via esterases in the body (DECOS 1993; ECETOC 2005a). 2-Methoxypropanol is then further metabolized to 2-methoxypropanoic acid, its principal metabolite. Health effects information available for these two substances is considered relevant to inform the health effects assessment of 2-methoxypropyl acetate.

2-Methoxypropanol has been assessed by Health Canada in a screening assessment under the CMP (EC, HC 2009). In that assessment, data on 2-methoxypropyl acetate and 2-methoxypropanoic acid were taken into consideration. A literature search was conducted for 2-methoxypropyl acetate, 2-methoxypropanol, and 2-methoxypropanoic acid from June 2007 (year of latest literature search in the screening assessment) to December 2020, and no additional health effects studies were identified. Further details of toxicity studies considered in this assessment are found in the screening assessment of 2-methoxypropanol. A summary of this information is provided below (EC, HC 2009).

Repeated-dose toxicity

Hematological effects were observed in male rats following 10 days of oral exposure (gavage) to 1800 mg 2-methoxypropanol/kg bw/day or 2600 mg 2-methoxypropyl acetate/kg bw/day (Ma-Hock et al. 2005). When rats were exposed via inhalation to 2-methoxypropyl acetate at concentrations of 0, 600, 3000, and 15 000 mg/m^3, 6 hours/day, 5 days/week for 28 days, hematological and biochemical alterations were observed at the highest dose. Thymus atrophy as well as reduced body weight gain and respiratory irritation were also observed at this concentration (Ma-Hock et al. 2005).

Reproductive/developmental toxicity

Developmental effects were observed in both pregnant rats and rabbits exposed to 2-methoxypropyl acetate by inhalation. Effects included significantly increased fetal resorption, thoracic vertebral incision and split vertebrae (in rats at 14 900 mg/m^3) and malformations of sternum, paws, major blood vessels and heart (in rabbits at 3000 mg/m^3). Maternal toxicity was also observed (significantly reduced maternal body weights, respiratory and eye irritation, and sedation in rats at 3000 mg/m^3 and 14 900 mg/m^3 and reductions in maternal body weights in rabbits at 3000 mg/m^3) (ECETOC 2005a).

Pregnant rabbits exposed via inhalation to 2-methoxypropanol for 6 hours/day from GD 6 to GD 18 demonstrated dose-related, significantly increased fetal resorption and incidence of fetal visceral and skeletal malformations/variations and significantly reduced fetal body weights starting at doses from 843 mg/m^3 in the absence of maternal toxicity. The author identified the NOAEC to be 543 mg/m^3 (equivalent to a NOAEC of 796 mg/m^3 for 2-methoxypropyl acetate on the basis of a molecular weight conversion assuming same molar amount). Pregnant rats exposed to higher concentrations of 2-methoxypropanol had fetuses with thoracic vertebral incisions and split vertebrae (BASF 1986).

No information on potential developmental toxicity via oral administration of 2-methoxypropyl acetate and 2-methoxypropanol was identified. In an oral gavage study conducted in pregnant rabbits using 2-methoxypropanoic acid from GD 7 to GD 19, significantly increased fetal resorption and incidence of fetal variations and malformations (missing ribs, delayed ossifications, retrocaval ureter and paraovarian cyst) were observed at 78 mg/kg bw/day (equivalent to 99 mg 2-methoxypropyl acetate/kg bw/day, based on molecular weight conversion assuming same molar amount), with a NOAEL of 26 mg/kg bw/day (equivalent to 33 mg 2-methoxypropyl acetate/kg bw/day) (Carney et al. 2003).

Genotoxicity

There are no genotoxicity studies available for 2-methoxypropyl acetate in the literature and only limited data are available on the genotoxicity of 2-methoxypropanol. It did not induce gene mutation in Ames tests with various *Salmonella* strains, with or without metabolic activation (BASF 1988).

Carcinogenicity

With regard to the potential carcinogenicity or chronic toxicity of 2-methoxypropyl acetate, no long-term study has been identified.

Characterization of risk

Once absorbed, 2-methoxypropyl acetate is rapidly hydrolyzed to 2-methoxypropanol via esterases in the body (DECOS 1993; ECETOC 2005a). Available information for 2-methoxypropanol, and its principal metabolite, 2-methoxypropanoic acid, was therefore considered relevant to inform the health effects characterization of 2-methoxypropyl acetate.

The critical effect for characterization of risk to human health for 2-methoxypropyl acetate is developmental toxicity. Furthermore, 2-methoxypropyl acetate has been classified as reproductive toxicant (Repr 1B, may damage the unborn child) in the harmonized classification and labelling table in Annex VI to the Classification, Labelling, and Packaging (CLP) Regulation (ECHA 2008).

A NOAEC of 543 mg/m^3 for 2-methoxypropanol was identified in a developmental study of rabbits exposed via inhalation. The equivalent NOAEC for 2-methoxypropyl acetate was determined to be 796 mg/m^3 on the basis of a molecular weight conversion assuming same molar amount. At the next dose (843 mg/m^3), the effects were a significant increase in fetal resorption and in incidence of fetal visceral and skeletal malformations/variations and a significant reduction in fetal body weights, in the absence of maternal toxicity (Hellwig et al. 1994). For the oral route, the critical effect level was identified to be a NOAEL of 26 mg 2-methoxypropanoic acid/kg bw/day (equivalent to 33 mg 2-methoxypropyl acetate/kg bw/day on the basis of a molecular weight conversion assuming same molar amount) from a developmental study in which pregnant rabbits were administered 2-methoxypropanoic acid via gavage. In this study, fetal resorption and incidence of fetal variations and malformations, such as missing ribs, delayed ossifications, retrocaval ureter, and paraovarian cyst, were observed at 78 mg 2-methoxypropanoic acid/kg bw/day (equivalent to 99 mg 2-methoxypropyl acetate/kg bw/day) (Carney et al. 2003).

The general population may be exposed to 2-methoxypropyl acetate through environmental media, mainly air and water. Concentrations of 2-methoxypropyl acetate in environmental media were estimated from modelling approaches using an estimated total volume of PMA in commerce and assuming that 2-methoxypropyl acetate is present as a potential impurity (up to 0.5%) in PMA.

It was assumed that the general population of Canada may also be exposed to 2-methoxypropyl acetate when using various products containing PMA with 2-methoxypropyl acetate as a potential impurity. Cosmetics containing up to 10% PMA and aerosol paints and putty fillers containing up to 20% PMA were identified as representative products. Table 7-6 provides relevant exposure and hazard values for 2-methoxypropyl acetate as well as resultant margins of exposure (MOEs) for the characterization of risk.

Table 7-6. Relevant oral and inhalation exposure estimates, critical effect levels and resulting margins of exposure for 2-methoxypropyl acetate

Exposure scenario	Exposure	Critical effect level	Critical health effect endpoint	MOE
Total exposure from environmental media	0.00044 mg/kg bw/day	NOAEL = 33 mg/kg bw/day	Significantly increased fetal resorption and incidence of fetal variations and malformations	75 000
Nail polish (estimated high end inhalation scenario for cosmetics (0.05%) (inhalation intermittent)	0.012 mg/m^3	NOAEC = 796 mg/m^3 [a]	Significant increase in fetal resorption and incidence of fetal visceral and skeletal malformations/variations and significant reduction in fetal body weights	66 333
Aerosol paint (inhalation intermittent)	0.25 mg/m^3	NOAEC = 796 mg/m^3 [a]	Significant increase in fetal resorption and incidence of fetal visceral and skeletal malformations/variations and significant reduction in fetal body weights	3184
Putty filler (inhalation intermittent)	0.48 mg/m^3	NOAEC = 796 mg/m^3 [a]	Significant increase in fetal resorption and incidence of fetal visceral and skeletal malformations/variations and significant reduction in fetal body weights	1658

Abbreviations: MOE, margin of exposure; NOAEC, no-observed-adverse-effect concentration; NOAEL, no-observed-adverse-effect level

[a] Molecular weight conversion from NOAEC = 543 mg/m^3

On the basis of the conservative approaches used in estimating exposure to 2-methoxypropyl acetate from environmental media and modelling inhalation exposure from the use of products available to consumers, it is considered that the calculated MOEs are adequate to account for uncertainties in the health effects and exposure datasets.

While exposure of the general population to 2-methoxypropyl acetate is not of concern at current levels, this substance is considered to have a health effect of concern on the basis of its potential for developmental toxicity. Therefore, there may be a concern for human health if exposures to 2-methoxypropyl acetate were to increase.

7.2 Subgroup B: Esters of di/tri- ols

7.2.1 Triacetin

Exposure assessment

As triacetin is considered to be of low hazard potential (see Health effects assessment below), quantitative estimates of exposure to the general population were not derived. This section provides general information on exposure to triacetin.

Triacetin is a liquid with a moderate vapour pressure and very high water solubility. The Henry's law constant indicates that triacetin is expected to be essentially non-volatile from water surfaces, and volatilization from moist soil surfaces is not an important fate process (HSDB 1983-).

Won and Lusztyk (2011) present summary data for triacetin measured in indoor air in homes in Quebec City using passive sampling between November 2008 and March 2010. Triacetin was detected in 76% of the samples, and the geometric mean and maximum reported concentrations in indoor air were 0.52 μg/m^3 and 7.77 μg/m^3, respectively. Triacetin was also identified to be present in household dust collected from 50 dust samples from homes in Quebec City (Won and Lusztyk 2011). The geometric mean concentration of triacetin in dust samples was reported to be 0.77 µg/g dust (detection frequency of 26%) with a maximum value of 8.6 µg/g. Measured concentrations of triacetin in ambient air or water in Canada were not identified.

Triacetin is a permitted food additive for use as prescribed on the *List of Permitted Food Additives with Other Accepted Uses*, and the *List of Permitted Carrier or Extraction Solvents*, incorporated by reference into their respective Marketing Authorization issued under the *Food and Drugs Act*. It has been evaluated as a flavouring substance by JECFA, which concluded that the substance posed “no safety concern” based on current levels of intake when used as a flavouring agent (JECFA 2002). However, there is no definitive information available concerning the potential use of triacetin as a food flavouring agent in Canada. Triacetin may be used as a component in an incidental additive (lubricant) in food processing establishments with no potential for direct food contact, and therefore dietary exposure is not expected (personal communication, email from FD, HC, to ESRAB, HC, dated December 5, 2016; unreferenced).

This substance is found in over 100 cosmetics in Canada, including adhesives, cleansers, exfoliants, makeup, makeup removers, massage products, and nail polishes. Concentrations range from less than 0.1% to 30% (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Use of these products may result in dermal or inhalation exposure to the general population in Canada.

Triacetin is used as a non-medicinal ingredient in more than 400 natural health products in Canada. Most products are taken via the oral route, with a small number of topical, dental, and sublingual applications (personal communication, email from NNHPD, HC, to ESRAB, HC, dated December 6, 2016; unreferenced). Triacetin is also used as a non-medicinal ingredient in more than 25 prescription and/or non-prescription drugs including topical, subcutaneous, transdermal, oral, vaginal and intracervical applications (personal communication, email from TPD, HC, to ESRAB, HC, dated December 6, 2016; unreferenced), resulting in exposure to those within the general population in Canada that may use these products.

Health effects assessment and characterization of risk

OECD (2002) summarized the health effects literature for triacetin. This assessment was used to inform the health effects characterization in this screening assessment.

A literature search was conducted from the year prior to the OECD SIAR (January 2001) to December 2020. No health effects studies that could result in a different health effects characterization from that of the OECD (2002) were identified.

Triacetin was considered by the OECD to have a “low hazard potential” based on the available dataset. There were no treatment-related adverse effects observed in experimental animals in repeated-dose oral and inhalation toxicity studies, at any of the oral doses (up to 10 000 mg/kg bw/day) or concentrations (2220 mg/m^3 to 73 700 mg/m^3 [saturation]) tested. No adverse effects were observed in a combined oral repeated-dose and reproductive/developmental toxicity screening test in which doses were tested at up to and including the limit dose of 1000 mg/kg bw/day. Also, taking all data into consideration, triacetin was considered non-genotoxic *in vitro*. No data were available on the carcinogenicity of this substance.

As mentioned in OECD (2002), the JECFA considers it unnecessary to assign an acceptable daily intake (ADI) for triacetin since this substance is metabolized like other triglycerides in food. JECFA concluded that based on the available data and anticipated daily intake, triacetin did not represent a hazard to health (OECD 2002). More recently, the EU’s Scientific Committee for Food endorsed this position in their evaluation of triacetin (OECD 2002).

The OECD did not identify effects of concern for human health and classified triacetin as low priority for further work. As such, it is considered to be of low hazard potential, and therefore characterization of exposure potential (i.e., derivation of exposure estimates) was not considered to be warranted. The risk to human health is considered to be low.

7.2.2 C14-22 monoglycerides

Exposure assessment

Given that C14-22 monoglycerides are considered to be of low hazard potential (see Health effects assessment below), quantitative estimates of exposure to the general population were not derived. This section provides general information on exposure to C14-22 monoglycerides.

Exposure to C14-C22 monoglycerides by the general population of Canada is expected to be mainly via the oral route through food ingestion resulting from their use as permitted food additives in Canada.

C14-22 monoglycerides are included in the listings for two approved food additives in Canada, monoglycerides and mono- and di-glycerides, as set out in the List of Permitted Food Additives, and would therefore be an acceptable food additive for these approved uses in Canada. Mono- and diglycerides have been listed by the US FDA as substances affirmed as generally recognized as safe (GRAS) as direct human food ingredients (US eCFR 2017).

C14-22 monoglycerides may be used as a component in the manufacture of food packaging materials that are in direct contact with food. However, dietary exposure is expected to be minimal compared to exposure from use as a permitted food additive. It may also be used as a component in incidental additives (e.g., lubricants and release agents) in food processing establishments. Dietary exposure, if any, is considered to be negligible (personal communication, email from the FD, HC, to ESRAB, HC, dated November 23, 2015; unreferenced).

Health effects assessment and characterization of risk

No health effects studies on C14-22 monoglycerides were identified.

In the body, monoglycerides are metabolized like other triglycerides of food fats. Monoglycerides are metabolized to free fatty acids and glycerol, both of which are then available for the resynthesis of triglycerides in the intestinal mucosa. There is no evidence that the presence of monoglycerides or diglycerides of food fats has any deleterious effect on cells or tissues. In humans, mono- and diglycerides are consumed every day in any normal mixed diet and are also formed during the digestion and absorption of meals containing fat. No harmful effects have been specifically associated with mono- and diglycerides (WHO 1974). Consequently, JECFA assigned an acceptable daily intake (ADI) without an explicit indication of the upper limit of intake (“not limited”) to mono- and diglycerides (WHO 1974).

C14-22 monoglycerides are considered to be of low hazard potential, and characterization of exposure potential (i.e., derivation of exposure estimates) was not considered to be warranted. The risk to human health is considered to be low.

7.3 Subgroup C: Esters of 2,2,4-trimethylpentane-1,3-diol with isobutyric acid

7.3.1 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate

Exposure assessment

Environmental media

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is a liquid with a moderate vapour pressure. Summary data for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate measured in indoor air in homes in Quebec City using passive sampling between November 2008 and March 2010 were presented by Won and Lusztyk (2011). Concentrations in indoor air ranged from 0.5 to 200.5 $\mu g/m^3$, with a geometric mean concentration of 6.55 $\mu g/m^3$ (and geometric standard deviation of 2.47). Won and Lusztyk (2011) noted emissions of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from water-based paints, acrylic floor polish, acoustic ceiling tiles, and polyurethane foam underpads. 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate has also been measured in emissions from solid building materials (vinyl flooring, carpet, carpet underpads, flooring adhesive composite, and polyurethane foam) up to 10,000 $\mu g/m^2/h$, as well as from liquid building materials (paint, primer, stains, varnish, caulking) up to 77 $\mu g/m^2/h$ (Won and Yang 2012). Won and Yang (2012) also noted emissions from products for consumers, such as artistic oil paints and candles, up to rates of 0.24 $\mu g/m^2/h$.

Internationally, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate was also measured in indoor air in several studies in the United States, Germany, Iceland, Estonia and Sweden, in sites including typical homes, newly manufactured and built homes, temporary housing units, storage rooms and classrooms (Sahlberg et al. 2013; Kim et al. 2007; Wieslander et al. 1997; Hodgson et al. 2000; Maddalena 2009; Markowicz and Larsson 2015; Choi et al. 2010). Average air concentrations from these studies ranged from 1.5 $\mu g/m^3$ to 73 $\mu g/m^3$.

In Sweden, two studies have examined personal air sampling for painters during an 8-hour working day (Norbäck et al. 1995; Wieslander and Norbäck 2010), with reported geometric mean concentrations ranging from 6 $\mu g/m^3$ to 10 $\mu g/m^3$ and maximum values of 14 $\mu g/m^3$ and 40 $\mu g/m^3$, respectively.

The highest Canadian indoor air concentration value for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate based on indoor air monitoring in Quebec City (200.5 μg/m^3) was used to estimate general population exposure.

Ambient air concentrations were collected at the same time as classroom indoor air in eight schools in Sweden (Kim et al. 2007). Eight 4-hour ambient samples were collected with values ranging from 0.24 μg/m^3 to 0.75 μg/m^3 and a mean concentration of 0.41 μg/m^3. No Canadian ambient air measurements for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate were identified. As a conservative approach, the maximum Canadian indoor air concentration value (200.5 μg/m^3) was applied to ambient air to estimate daily exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in the general population in Canada from environmental sources.

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is estimated to have moderate water solubility. Based on an estimated Henry's law constant value of 1.1×10^{-5} atm-m^3/mol, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate is expected to volatilize from water surfaces (HSDB 1983-). No data measuring 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in water in Canada were identified.

Fifty dust samples were collected from residences in Quebec City (Won and Lusztyk 2011). 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate was detected in 62% of the samples with a reported concentration range of 1.0 μg/g to 715 μg/g and a geometric mean value of 21.2 μg/g. The maximum concentration value in dust from this Canadian study (715 μg/g) was used as an input to estimate daily intake of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate to the general population from environmental sources.

General population exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from ambient air, indoor air and dust ranged from 41 to 148 μg/kg bw/day (see Table B-3, Appendix B). The highest exposed age group was 1-year-olds, and indoor air was identified as the greatest source of environmental exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate.

Food

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate may be used as a component in the manufacture of food packaging materials, with no direct food contact, and therefore dietary exposure is not expected (personal communication, e-mail from FD, HC, to ESRAB, HC, dated December 5, 2016, and March 15, 2021; unreferenced).

Biological monitoring

Two metabolites of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (specifically 2,2,4-trimethyl-1,3-pentanediol [TMPD] and 2,2,4-trimethyl-3-hydroxyvaleric acid [HTMV]) were analyzed in the urine in participants aged 3 to 79 years in cycle 5 (2016–2017) of the Canadian Health Measures Survey (CHMS). The toxicokinetics of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in humans are not well studied. Animal studies indicate that the metabolites are mainly excreted in urine within 72 hours; a smaller fraction is eliminated in feces over a span of approximately 1 week (CIR 2017, as cited in Health Canada 2019). Animal studies report that 2,2,4-trimethyl-1,3-pentanediol diisobutyrate is predominantly excreted as the *O*-glucuronide of TMPD in urine, and to a much lesser extent as HTMV and its glucuronides, 2-methylmalonic acid, and unchanged 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (CIR 2017, as cited in Health Canada 2019). Data from cycle 5 of the CHMS indicate a detection frequency of greater than 95% in all population groups. The geometric mean urine concentration of TMPD (primary metabolite) for ages 3 to 79 years is 17 μg/L and the 90th percentile is 69 μg/L. The highest concentrations of TMPD are found in children aged 3 to 5 years (25 μg/L geometric mean; 140 μg/L 95th percentile) followed by children aged 6 to 11 years (23 μg/L geometric mean; 74 μg/L 90th percentile).

Products available to consumers

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is found in adhesives (eye), nail moisturizers, nail polishes, and nail polish removers in Canada (personal communication, emails from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced).

Dermal and inhalation exposure estimates were derived for these products at the highest notified concentration levels. As inhalation exposure to cosmetics was found to contribute less than 1% of the overall exposure, only dermal exposure estimates are presented.

Table 7-7 summarizes the dermal exposure estimates for cosmetics containing 2,2,4-trimethyl-1,3-pentanediol diisobutyrate based on sentinel scenarios (i.e., those product/concentration/age group combinations with the highest exposures). Details on the method and parameters used to estimate dermal exposures to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from cosmetics are available in Appendix C-3.

Table 7-7. Estimated dermal exposures to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from the use of cosmetics

Product scenario	**Substance conc.[a]**	**External dermal exposure[b] (mg/kg bw/day)**
Adhesive (eye) (based on mascara scenario; 4-8 years)	30%	0.23
Nail polish (2-3 years)	30%	1.2
Nail polish remover (9-13 years)	1%	0.54

Abbreviation: conc., concentration

[a] Personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced.

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is also found as a non-medicinal ingredient for the purpose of being a plasticizer in one natural health product, a topically-applied wart remover. Exposure to this product was estimated assuming an application of approximately 0.1 mL (equivalent to 2 drops/day) and a concentration of 20% of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (based on the concentration of the medicinal ingredient [27%] and considering the other non-medicinal ingredients present in the product), resulting in 0.86 mg/kg bw/day and 0.48 mg/kg bw/day for 4- to 8-year-olds and 9- to 13-year-olds, respectively.

The general population of Canada may also be exposed to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate when using various products containing the substance including aerosol primers, pool paints, liquid hardeners/fiberglass resin repair kits, concrete crack repair kits, floor polishes and hobby paints (SDS 2012, 2013, 2015f, 2015g, 2016b, 2017d, 2017e). Table 7-8 summarizes inhalation and dermal exposure estimates for products available to consumers containing 2,2,4-trimethyl-1,3-pentanediol diisobutyrate. Details on the method and parameters used to estimate exposures to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from cosmetics are available in Appendix C-3.

Table 7-8. Estimates of exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from use of products available to consumers

Product scenario	Substance conc.	Inhalation exposure (mg/kg bw/day)	External dermal exposure (mg/kg bw/day)	Total exposure[a] (mg/kg bw/day)
Aerosol primer[b] (19+ years)	5%	0.24	1.01	1.24
Marine/pool paint (19+ years)	5%	N/A	3.6	3.6
Liquid hardener; fiberglass repair kit (m/l and apply) (19+ years)	30% (0.5% during application)	0.014	0.21	0.22
Concrete crack repair product (19+ years)	40%	0.025	0.27	0.30
Hobby paint (2-3 years)	3%	N/A	0.1	0.1

Abbreviations: conc., concentration; N/A, not applicable

[a] Total exposure estimate is the combination of inhalation and dermal routes and assumes inhalation and dermal absorption is equivalent to absorption following oral intake.

[b] Based on spray model inputs as evaporation model resulted in lower air concentration estimates. Total exposure also includes oral (non-inhaled) particles.

Exposure estimates presented in Table 7-8 were considered to address other scenarios expected to result in lower exposure potential including use of marine hardener (2,2,4-trimethyl-1,3-pentanediol diisobutyrate concentration in product up to 60%, but small use volume [less than 1 mL]) and floor polish (2,2,4-trimethyl-1,3-pentanediol diisobutyrate concentration up to 0.5%, but applied with mechanical applicator).

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is used as a plasticizer and has been found in a range of articles, including products available to children.

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate has also been shown to migrate from baby bottles made from materials used as substitutes for polycarbonate in a study of baby bottles purchased in Belgium (Onghena et al. 2016), as well as from those available in the EU market originating from several countries, including Canada (although the specific details for the Canadian samples were not provided) (Simoneau et al. 2012).

Simoneau et al. (2012) examined 277 baby bottles made of various materials including polypropylene, polyamide, polycarbonate, polyethersulfone, a new co-polyester (Triton^{TM}), and silicone purchased from 26 EU countries, Canada, Switzerland and the United States. In this study, identified as a screening study of the potential release of substances from different types of baby bottles, the bottles were sterilized prior to migration testing, and testing was performed using the protocols prescribed in the EU Regulation 10/2011 (hot fill conditions, 2 hours at 70°C) and 50% ethanol as simulant for milk. Second and third migration tests were performed. 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate migration was associated with bottles made of polypropylene, silicone and polyamide. 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate concentrations were between 1 µg/kg and 62 µg/kg, with an average of 5 µg/kg for polypropylene (72/149 detects), between 14 µg/kg and 574 µg/kg with an average of 159 µg/kg for the silicone bottles (5/5 detected), and 2 µg/kg in 3/28 polyamide bottles.

In a study by Onghena et al. (2016), 6 bottles were analyzed in a variety of tests (e.g., microwave, steam sterilization and dishwater tests). 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate was measured at 348 µg/kg in a silicone bottle using conventional EU repetitive-use migration conditions. Concentrations ranged from less than the limit of quantification (LOQ) (6.4 µg/kg) to 13 µg/kg (from a silicone bottle) in microwave heating tests and from less than the LOQ (6.4 µg/kg) to 247 µg/kg (first migration step) in the cook sterilization treatment. The highest concentration of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate for the 10th repetition of any treatment was 128 µg/kg for the cook sterilization cycle.

Oral exposure of infants aged 0 to 1 month associated with the migration of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from baby bottles was estimated to range from 57.5 µg/kg bw/day to 96.4 µg/kg bw/day (details presented in Appendix C-1).

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate was identified (but not quantified) in 15 of 47 polyvinylchloride (PVC) toys (Bouma and Schakel 2002). 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate was measured to be 21 μg/g in the outer material palm of a mitten designed for 2-year-olds in a Danish survey examining chemicals in products available to consumers (Tonning et al. 2009). Summary results of migration measurements for three non-phthalate plasticizers, including 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, from 12 different types of children's toys were also reported by Janssen and Bremmer (2009). In this report, the migration values were determined by immersing circular samples of the toys in saliva simulant rotated at 60 rpm for 60 minutes at 20°C. The mean and maximum migration for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate was reported to be 0.87 μg/min × 10 cm^2 and 2.25 μg/min × 10 cm^2, respectively. The US Consumer Product Safety Commission (CPSC) also measured migration of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from plastic child care articles. The maximum average migration was 11.3 μg/min × 10 cm^2 (US CPSC 2010).

Oral exposure to young children (aged 6 months to 1 year) from mouthing of plastic toys containing PVC was estimated to be 149 μg/kg bw/day (details presented in Appendix C-2). Dermal and hand-to-mouth exposure to children (1 year) handling toys was also estimated based on the same migration information. Total exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in children aged 1 year was estimated to be 1849 μg/kg bw/day (details presented in Appendix C-2).

In Canada, materials emissions were measured for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in various materials, including acoustic tiles, water-based paint, acrylic floor polishing, polyurethane foam underpad and vinyl sheets (Won and Lusztyk 2011). Chamber air concentrations ranged from 11.7 μg/m^3 to 418.7 μg/m^3 at 24 hours (Won and Lusztyk 2011). These exposures are considered to be captured by the other scenarios in Table 7-8, e.g., aerosol primer, which result in exposures likely higher than those from building materials.

Health effects assessment

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate has been reviewed by the OECD (1995), and this review was used to inform the health effects characterization for this substance. The OECD considered 2,2,4-trimethyl-1,3-pentanediol diisobutyrate to be of low potential risk and of low priority for further work.

A literature search was conducted for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from the year prior to the OECD review (i.e., January 1994) to December 2020. New health effects studies were identified and are considered in this assessment.

Repeated-dose toxicity

There are no repeated-dose studies available for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate following inhalation and dermal exposure. The health effects of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from oral exposure were studied in rats (n = 12 animals/group) in a combined repeated-dose and reproductive/developmental toxicity screening test conducted according to OECD guidelines. In this study, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate was administered by gavage at doses of 0, 30, 150, and 750 mg/kg bw/day, 7 days/week. In male rats, the exposure period was 44 days, including 12 days before mating (2 weeks prior to mating, 2 weeks of mating and 2 weeks after the completion of the mating period). In females, the exposure period was from 14 days before mating to day 3 of lactation. Increases in creatinine and total bilirubin were observed in rats administered 150 mg/kg bw/day and 750 mg/kg bw/day, and increases in total protein were observed in male rats at 750 mg/kg bw/day. Increases in liver weight were observed in male rats at 150 mg/kg bw/day and 750 mg/kg bw/day, and increases in incidence of brown coloured livers were noted in male rats exposed to the highest dose. However, histopathological changes were not reported in the liver. Increases in kidneys weights were observed in male rats at the highest dose. Histopathological findings observed in kidneys included increases in the grade of basophilic changes of the renal tubular epithelium and degeneration of hyaline droplet in male rats at the two highest doses. In males exposed to the highest dose, necrosis and fibrosis of the proximal tubule, dilatation of the distal tubule, and decreased fatty changes were also observed. These effects are considered to be specific to male rats and are not considered adverse. Slight swelling of the liver cells was also noted at that dose level (OECD 1995). A no-observed-effect level (NOEL) of 30 mg/kg bw/day and a lowest-observed-effect level (LOEL) of 150 mg/kg bw/day were identified by the OECD, on the basis of liver and kidney effects in parental animals.

Since the OECD review was published in 1995, a subchronic oral study has been conducted in a larger sample of rats with 2,2,4-trimethyl-1,3-pentanediol diisobutyrate. Test animals (20/sex/dose) were fed diets containing 0, 30, 150, and 750 mg/kg bw/day of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate for 90 days. In males, cholesterol, bilirubin, and creatinine levels were statistically increased at the highest dose. A significant increase in relative kidney weight and a significant increase in incidence of hyaline droplets and in incidence (but not severity) of chronic progressive nephropathy were also observed in males at 750 mg/kg bw/day. Hyaline droplets in the kidney were also observed at lower doses. The finding was not considered adverse by the study authors as male rats are predisposed to this condition. No kidney effects were noted in females in any group. At 750 mg/kg bw/day in females, effects were limited to a statistically significant increase in cholesterol levels. The authors identified a LOEL of 750 mg/kg bw/day for males and a NOAEL of 750 mg/kg bw/day for females (Anonymous 1981, as cited in ECHA c2007-2017z). However, since the effects in males were not considered to be adverse, a NOAEL of 750 mg/kg bw/day was determined for both male and female rats from this study.

Reproductive/developmental toxicity

In the combined repeated-dose and reproductive/developmental toxicity test described earlier, no effects related to mating, fertility and estrous cycle were noted by the authors of the study at any dose tested. No other treatment-related effects were observed in dams during the pregnancy and lactation period and in pups after their birth (OECD 1995).

Since the OECD review (1995), a reproductive/developmental toxicity screening test and a developmental toxicity study (both conducted following OECD guidelines) have been conducted in rats with 2,2,4-trimethyl-1,3-pentanediol diisobutyrate. In the former study, test animals (12/sex/dose) were fed diets containing 0, 1.5, 4.5, and 15 mg of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate per gram of feed (dose levels in males and females calculated from dietary concentrations were 0, 91/120, 276/359 and 905/1135 mg/kg bw/day, respectively) (Study Submission 2001; Anonymous 2001, as cited in ECHA c2007-2017za). All male rats were treated from the beginning of the premating period to the final treatment of the female rats for a total of 51 days. Females were treated from the beginning of the premating period to day 4 of lactation for a total of 40 to 51 treatments.

Reproductive effects, such as a statistically significant reduction in the mean number of implantation sites and a non-statistically significant decrease in the number of corpora lutea, were observed in animals treated with 905/1135 mg/kg bw/day, the highest dose tested. At this dose level, mean litter weights were also decreased by 19% to 20% on post-natal day (PND) 0 and 4 and the number of live pups per litter was 17% lower on PND 4 (12.0 in the high-dose group vs 14.5 in the control group; $p \leq 0.05$). The mean number of pups dying between PND 0 and 4 was higher for litters from the mid-dose and high-dose groups, but the increase was not dose-related and was statistically significant at the mid-dose only (0.5 ± 0.7 at mid-dose vs. 0.0 ± 0.0 for control animals and 0.2 ± 0.4 at highest dose). These findings are of unclear relevance since no clear trend was identified. No changes were reported for any other examined parameters.

These reproductive effects were observed in presence of systemic toxicity in parental animals. Transient decreases in body weight gain and food consumption were noted in adults exposed to the highest dose on day 7 of the pre-mating phase. Mean body weight gains were significantly decreased by 27% and 48% and food consumption was reduced by 15% and 21% in male and female rats, respectively. Minimal reductions in sperm counts were seen in the testes and/or epididymides of treated male rats, but these reductions were not considered toxicologically significant by the authors (Anonymous 2001, as cited in ECHA c2007-2017za). An expert review of the study also confirmed the non-relevance of these findings (Eastman 2007).

Overall, the critical effect level identified by the authors for this reproductive toxicity study was a NOAEL of 276 mg/kg bw/day in males and 359 mg/kg bw/day in females. They were based on a statistically significant reduction in the mean number of implantation sites and a non-significant decrease in the number of corpora lutea at the highest dose tested (equivalent to 1135 mg/kg bw/day for females) (Anonymous 2001, as cited in ECHA c2007-2017za).

In a prenatal developmental toxicity study conducted according to OECD Test Guideline 414, female rats were exposed through the diet to 0, 0.15, 0.45, or 1.50% 2,2,4-

trimethyl-1,3-pentanediol diisobutyrate (0, 118, 343, or 1077 mg/kg bw/day, respectively) from GD 0 to GD 20. The NOAEL for maternal toxicity, fetal growth and developmental toxicity was determined by the authors to be 343 mg/kg bw/day. At the highest dose tested (1077 mg/kg bw/day), significantly lower mean body weight and significantly reduced mean food consumption were observed in dams for the entire exposure period. A significant and dose-dependent decrease in mean male, female and combined fetal body weight was noted in offspring of the high-dose group compared to the control group. Effects on fetal body weight at 1077 mg/kg bw/day were observed in presence of maternal toxicity. There were no test substance-related external and visceral malformations or developmental variations noted (Anonymous 2015, as cited in ECHA c2007-2017zb).

In a report of another prenatal developmental toxicity study, New Zealand White rabbits (n = 22/group) were gavaged with 0, 100, 300, or 1000 mg/kg bw/day 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from GD 1 to GD 28 (Anonymous 2018, as cited in ECHA c2007-2020b). The mean number of early resorptions and thus post-implantation losses were outside historical ranges at 1000 mg/kg bw/day. However, details on statistical significance were not provided and the effect was described as resulting in a “slightly” lower mean live litter size only. In surviving fetuses, no effects on growth or development were observed. The report authors identified a NOAEL of 300 mg/kg bw/day on the basis of reduced embryo/fetal survival at the next dose level of 1000 mg/kg bw/day.

Genotoxicity

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate did not induce mutagenicity in bacteria and did not induce chromosome aberrations in mammalian cells (OECD 1995). 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is considered as non-genotoxic (EFSA 2006).

Carcinogenicity

No carcinogenicity or chronic toxicity studies were identified in the literature for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate.

Characterization of risk

No carcinogenicity studies were identified in the literature for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate. No genotoxicity was observed in the available empirical data for this substance. On the basis of the available information, critical effects associated with 2,2,4-trimethyl-1,3-pentanediol diisobutyrate are considered to be reproductive effects.

In a reproductive/developmental toxicity screening test, a NOAEL was set at 276 mg/kg bw/day in males and 359 mg/kg bw/day in females on the basis of a statistically significant reduction in the mean number of implantation sites and non-significant decrease in the number of corpora lutea observed at the next dose (1135 mg/kg bw/day for females) (Study Submission 2001; Anonymous 2001, as cited in ECHA c2007-2017za). However, in a combined repeated-dose and reproductive/developmental toxicity study, no adverse effects were observed in experimental animals administered doses of up to 750 mg/kg bw/day (i.e., NOAEL of 750 mg/kg bw/day) (OECD 1995). The previous study (i.e., reproductive/developmental toxicity screening test) did not include a dose level of 750 mg/kg bw/day for testing; it only examined effects at 276/359 mg/kg bw/day, and then at 905/1135 mg/kg bw/day. Since the examined parameters and exposure duration between these two studies were similar (approximately 6 to 8 weeks), the higher NOAEL of 750 mg/kg bw/day was selected for reproductive toxicity for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate on the basis of reproductive effects occurring at a maternal oral dose of 1135 mg/kg bw/day (Anonymous 2001, as cited in ECHA c2007-2017za).

The predominant route of exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from environmental media for the general population is through indoor air. The general population of Canada may also be exposed to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate when using various products containing the substance, including nail products, cosmetic adhesives, aerosol primer, pool paint, liquid hardeners/fiberglass resin repair kits, concrete repair kits, and hobby paint. Oral exposure to children may also result from 2,2,4-trimethyl-1,3-pentanediol diisobutyrate contained in plastic baby bottles and plastic toys.

Biological monitoring data from cycle 5 of the CHMS demonstrate that metabolites of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate are prevalent in the urine of people aged 3 to 79 years in Canada. The pharmacokinetic data are limited and prevent the reliable use of the biological monitoring data in a quantitative risk characterization. Exposure estimates based on modelling will therefore be used to characterize the risk to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate.

Relevant exposure estimates, critical health effects levels, and resulting MOEs for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate are presented for adults/teens and children in Table 7-9 and Table 7-10, respectively.

Table 7-9. Relevant exposure estimates and resultant margins of exposure for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate compared to a critical effect level of 750 mg/kg bw/day[a]

Exposure scenario	Exposure[b](mg/kg bw/day)	Margin of exposure (MOE)
Total exposure from environmental media (1 year old) (chronic)	0.148	5 067
Cosmetic eye adhesive (14–18 years) (dermal chronic)	0.09	8 333
Nail polish (9–13 years) (dermal intermittent)	0.77	974

Exposure scenario	Exposure[b](mg/kg bw/day)	Margin of exposure (MOE)
Nail polish remover (14–18 years) (intermittent)	0.36	2 083
Aerosol primer (19+ years) (intermittent)	1.24	604
Marine/pool paint (19+ years) (dermal intermittent)	3.6	208
Liquid hardener/ fiberglass repair (19+ years) (intermittent)	0.22	3 409
Concrete crack repair (19+ years) (intermittent)	0.30	2 500
Hobby paint (19+ years) (dermal intermittent)	0.05	15 000
Non-medicinal ingredient for the purpose of plasticizer in a wart remover (9–13 years) (dermal short-term)	0.48	1 562

Abbreviation: MOE, margin of exposure

[a] Critical effect level (750 mg/kg bw/day) is determined on the basis of statistically significant reduction in the mean number of implantation sites and decrease in the number of corpora lutea at the next dose of 1135 mg/kg bw/day in an oral reproductive toxicity study

[b] Dermal absorption is assumed to be equivalent to absorption following oral intake

Table 7-10. Relevant exposure estimates and resultant margins of exposure for children to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate compared to a critical effect level of 750 mg/kg bw/day[a]

Exposure scenario	Exposure (mg/kg bw/day)	Margin of exposure (MOE)
Baby bottles (0- to 1-month-old) (oral chronic)	0.058 - 0.096	12 931 – 7 812
Children mouthing plastic toys (1-year-old) (oral chronic)	0.15	5 000
Children with dermal and hand-to-mouth contact with plastic toys (1-year-old) (oral chronic)	1.85	405
Cosmetic eye adhesive (4–8 years) (dermal chronic)	0.23	3 261
Nail polish (2–3 years) (dermal intermittent)	1.2	625
Nail polish remover (9–13 years) (dermal intermittent)	0.54	1 388
Non-medicinal ingredient for the purpose of plasticizer in a wart remover (4–8 years) (dermal short-term)	0.86	872

Abbreviation: MOE, margin of exposure

[a] Critical effect level (750 mg/kg bw/day) is determined on the basis of no adverse effects in oral repeated-dose studies in which animals were exposed at up to 750 mg/kg bw/day, the highest-dose tested (OECD 1995; Anonymous 2001, as cited in ECHA c2007-2017za)

On the basis of the conservative approaches used in estimating exposure, the margins between critical effects and estimates of exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate are considered adequate to account for uncertainties in the health effects and exposure datasets.

7.3.2 Texanol

Exposure assessment

As propanoic acid, 2-methyl-, monoester with 2,2,4-trimethyl-1,3-pentanediol, or texanol, is considered to be of low hazard potential (see Health effects assessment below), quantitative estimates of exposure to the general population were not derived. This section provides general information on exposure to texanol.

Texanol is a liquid with a moderate vapour pressure. Summary data for texanol measured in indoor air in homes in Quebec City using passive sampling between November 2008 and March 2010 were presented by Won and Lusztyk (2011). Concentrations of texanol in indoor air ranged from 0.36 $\mu g/m^3$ to 633.4 $\mu g/m^3$, with a geometric mean concentration of 13.4 $\mu g/m^3$. Texanol has also been measured in emissions from solid building materials (vinyl flooring and polyurethane foam) up to 132 $\mu g/m^2/h$ and from liquid building materials (paint, primer, stains, varnish, caulking, and adhesive) up to 127 $\mu g/m^2/h$ (Won and Yang 2012). Won and Yang (2012) also noted emissions from products for consumers, such as artistic oil paints and air deodorizer, up to emission rates of 74 $\mu g/m^2/h$. Through sampling in a microscale chamber, emission rates from an acrylic latex interior paint product were measured up to 88,837 $\mu g/m^2/h$ (Won et al. 2014).

No Canadian ambient air measurements for texanol were identified. No empirical data were found for texanol in water, dust or soil in Canada.

Texanol may be used as a component in the manufacture of food packaging materials, with no direct food contact. Therefore dietary exposure is not expected (personal communication, email from FD, HC, to ESRAB, HC, dated December 5, 2016; unreferenced).

In cosmetics, texanol functions as a plasticizer (European Commission 2008-) and is found in nail polish and makeup products in Canada at concentrations up to 10% (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Use of these products may result in dermal or inhalation exposure to the general population in Canada.

Texanol is used in a number of paint products (e.g., stains, sealants) and adhesive products available to consumers in Canada that may result in dermal or inhalation exposure (SDS 2015h, 2017f, 2017g).

Health effects assessment

Texanol has been reviewed by the OECD (1993), and this review was used to inform the health effects characterization for this substance. The OECD (1993) concluded that texanol has a relatively low order of toxicity and was also a low priority for further work.

A literature search was conducted for texanol from the year prior to the OECD (i.e., January 1992) to December 2020. New health effects studies were identified and are considered in this assessment.

Repeated-dose toxicity

There are no repeated-dose studies available for texanol following inhalation or dermal exposure. The OECD identified two oral studies which are described below.

Texanol was studied for oral toxicity in rats according to the OECD combined repeated-dose and reproductive/developmental toxicity test (OECD Test Guideline 422). Rats exposed by gavage at 0, 100, 300 and 1000 mg/kg bw/day for up to 51 consecutive days resulted in a NOAEL for both sexes of 1000 mg/kg bw/day with no significant treatment-related effects on mortality, clinical signs, body weight and body weight gain, feed consumption, or gross pathology in male rats. Centrilobular hepatomegaly was observed in the livers of rats at the two highest doses but this was considered an adaptive response since no degenerative changes were noted in this organ. Kidney lesions in male rats were typical of alpha 2-μ globulin nephropathy, and considered unique to rats and not likely relevant to humans (OECD 1993; Anonymous 1992, as cited in ECHA c2007-2017zc).

When rats (5/sex/dose) were administered texanol ester alcohol by gavage at 0, 100, and 1000 mg/kg bw/day, 5 days/week, for 11 days over a 15-day period, there were no significant treatment-related effects observed in either sex. A slight increase in liver weights was seen in both sexes at 1000 mg/kg bw/day. However, no treatment-related gross lesions or changes in clinical chemistry were observed in either sex and the minor hyaline droplet degeneration observed is a sex- and species-specific effect. Although a NOEL was identified to be less than 100 mg/kg bw/day for male rats and 100 mg/kg bw/day for female rats, the NOAEL was considered by the authors to be 1000 mg/kg bw/day for both sexes (OECD 1993; Anonymous 1984, as cited in ECHA c2007-2017zd).

Since the OECD (1993) review, a short-term oral study has been conducted in rats with texanol. In the study conducted according to the OECD Guideline 407, test animals (5/sex/group) were administered texanol daily by gavage at 0, 15, 150 and 1000 mg/kg bw/day for 28 days. The NOAEL for male/female systemic effects was established at

1000 mg/kg bw/day by the authors. No mortality, no treatment-related effects on body weight and food consumption, and no substance-related changes in clinical findings, clinical chemistry and hematology were observed. A statistically significant increase in liver weights was observed in female rats exposed to 1000 mg/kg bw/day, the highest dose tested. However, only minimal centrilobular hepatocyte enlargement was observed in 2 out of 5 female rats exposed to this dose level, which were considered to be adaptive and non-adverse. A dose-related increase in incidence and degree of cortical tubular eosinophilic inclusions was observed in male rats receiving 150 mg/kg bw/day (trace in 3 of 5 animals) and 1000 mg/kg bw/day (minimal in 2 of 5 animals and moderate in 3 of 5 animals) (Anonymous 1995, as cited in ECHA c2007-2017ze).

Reproductive/developmental toxicity

No reproductive/developmental toxicity studies were conducted with texanol via the inhalation or dermal route of exposure.

In the combined oral repeated-dose and reproductive/developmental toxicity test described earlier for texanol, no effect on mean number of live or dead pups/litter, total implants, prenatal loss, percent survival, total litter weight, mean pup weight, pup survival, external defects and postnatal growth was observed. The NOAEL for reproductive and developmental toxicity was the highest dose tested of 1000 mg/kg bw/day. No adverse effects were noted in parental animals. The NOAEL for systemic effects in the parental generation in this study was also 1000 mg/kg bw/day (OECD 1993; Anonymous 1992, as cited in ECHA c2007-2017zf).

Since the publication of the OECD review (1993), a developmental toxicity study was conducted in rats with texanol. In this OECD Guideline 414 study, female rats were administered 0, 100, 300 and 1000 mg/kg bw/day of texanol, by oral gavage, from GD 1-19. No effect on intrauterine growth, survival, and external, visceral, and skeletal fetal morphology was observed. The NOAEL for maternal toxicity was identified at 300 mg/kg bw/day on the basis of statistically significant reduction in mean food consumption and in mean body weight gain in dams at 1000 mg/kg bw/day. Reduction in food consumption was noted during GD 1-3 and 3-6 while the reduction in body weight gain was noted during GD 1-3 and 3-6 as well as for the entire dosing period (GD 1-19) (Anonymous 2015, as cited in ECHA c2007-2017zg).

Genotoxicity

Texanol showed negative results in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 and *Escherichia coli* WP2 uvrA/PKM101, with and without metabolic activation (Anonymous 1985, as cited in ECHA c2007-2017zh; Anonymous 1995, as cited in ECHA c2007-2017zi). Negative results were also reported *in vivo* in a mouse bone marrow micronucleus test in which groups of 5 males and 5 females were administered texanol once by gavage at doses of 0, 200, 1000, and 2000 mg/kg bw (OECD 1993; Anonymous 1992, as cited in ECHA c2007-2017zj).

Carcinogenicity

No carcinogenicity or chronic toxicity studies were identified in the literature for texanol.

Characterization of risk

No effects that were considered to be adverse were seen in repeated-dose (short-term and subchronic) or reproductive and developmental toxicity studies in which experimental animals were exposed orally to texanol at levels up to the limit dose of 1000 mg/kg bw/day. No carcinogenicity studies were identified in the literature for this substance, but texanol did not show any genotoxicity potential. The OECD (1993) concluded that texanol is associated with a relatively low order of toxicity and is a low priority for further work.

Considering the available health effects information, texanol is considered to be of low hazard potential, and therefore characterization of exposure potential (i.e., derivation of exposure estimates) was not considered to be warranted. The risk to human health is considered to be low.

7.4 Subgroup D: Individual – salt of a diester

7.4.1 Docusate sodium

Exposure assessment

Environmental media

Docusate sodium is a solid with a very low vapour pressure. If released to the atmosphere, it will exist primarily in the particulate phase (HSDB 1983-). In the vapour phase, it will degrade in the atmosphere by reaction with photochemically produced hydroxyl radicals with an estimated half-life of 18 hours (HSDB 1983-). The Henry's law constant for docusate sodium was estimated to be 5×10^{-12} atm-m^3/mol (EPI Suite c2000-2012), indicating that the substance is essentially non-volatile from water (HSDB 1983-).

No empirical data were identified for docusate sodium in air or water in Canada. Docusate sodium has been measured in surface water in the Gulf of Mexico following its use as a chemical dispersant to solubilize oil and minimize formation of surface oil slicks following the Deepwater Horizon oil release in 2010 (Gray et al. 2014). A study of inland water in a local community attempted to determine whether the presence of chemicals was associated with the chemical's use in the response to the Deepwater Horizon accident (Hayworth and Clement 2012). That study determined that docusate sodium present in water samples could be attributed to point and non-point source storm water discharge from 13 locations, and not from the accident response, with a maximum concentration of 19 ppb or 19 μg/L in the water samples.

Concentrations in Canadian surface water were estimated with the NSACB EAU Drinking Water Spreadsheets using the industrial release scenario (Health Canada 2015a). Details of model parameters are found in Appendix D. Using total imports of docusate sodium into Canada (Environment Canada 2013), the model modelled a surface water concentration of 5.6×10^{-4} mg/L.

Docusate sodium was not identified in soil or dust studies in Canada. Internationally, docusate sodium has been measured in soil (sand patties) following the Deepwater Horizon spill (McDaniel et al. 2015). These values were not considered relevant for general population exposure in Canada.

Food

Docusate sodium (listed as dioctyl sodium sulfosuccinate) is a permitted food additive for uses as prescribed on the *List of Permitted Food Additives with Other Generally Accepted Uses*, incorporated by reference into its respective Marketing Authorization issued under the *Food and Drugs Act*. Exposure to docusate sodium was estimated on the basis of its permitted use in sausage casings to reduce breakage (maximum 200 ppm in the casing) and as a wetting agent in fumaric acid-acidulated dry beverage bases (maximum 10 ppm in the finished beverage), as set out in the List of Permitted Food Additives.

Exposure estimates were derived for various age groups from the mean and 95th percentile consumption scenarios based on consumption of sausages and fruits drinks reported in the CCHS cycle 2.2 (2004), assuming that casings represent 1% of the weight of sausages and that all sausages and fruit drinks consumed contain docusate sodium at the maximum permitted level. The age group with the highest 95th percentile exposure values were children aged 2 to 3 years at 337.5 µg/kg bw/day. The estimated exposure to docusate sodium from food additive uses for the various age groups is presented in Table 7-11.

Table 7-11. Estimated human exposure to docusate sodium from food additive uses

	Estimated exposure (µg/kg bw/day)[a]							
Age group	**0 – < 6 months**	**6–11 months**	**1 year**	**2–3 years**	**4–8 years**	**9–13 years**	**14–18 years**	**19+ years**
Mean	-	-	49.5	66.4	64.2	48.1	28.3	8.2
95th percentile	-	-	270.7	337.5	274.5	210.0	134.2	58.6

[a] All persons mean and 95th percentile consumption of sausages and fruits drinks reported in the CCHS cycle 2.2.

The 95th percentile exposure values from food additive uses for the various age groups were combined with estimates of exposure from drinking water to estimate total daily intake for the general population in Canada (see Table B-4 of appendix B). The maximum total intake from all routes of exposure was 338 µg/kg bw/day for ages 2 to 3 years.

Docusate sodium may be used as a component in the manufacture of food packaging materials with no direct food contact, and therefore dietary exposure is not expected (personal communication, emails from FD, HC, to ESRAB, HC, dated December 5, 2016, and March 15, 2021; unreferenced).

General population exposure to docusate sodium from drinking water and food ranged from 0.05 µg/kg bw/day to 338 µg/kg bw/day (see Table B-4 Appendix B). The highest exposed population was the 2- to 3-year-old age group. Food appears to be a greater contributor to exposure than drinking water. However, the estimates for exposure to docusate sodium used as a food additive are considered to be conservative.

Products available to consumers

Docusate sodium functions as a cleansing agent, emulsifying agent, hydrotrope or surfactant in cosmetics (European Commission 2008-) and is found in more than 100 cosmetics in Canada, including adhesives, bath products, bleach, cleansers, exfoliants, fragrance products, hair colour, makeup (non-permanent), makeup remover, moisturizers, shampoos, shaving products, styling products and sunless tanning products (personal communication, emails from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced).

Dermal and inhalation exposure estimates were derived for these products at the highest concentration levels.

Table 7-12 summarizes the inhalation and dermal exposure estimates for cosmetics containing docusate sodium. Exposure estimates for adults and the youngest relevant age group for each product type are shown. Details on the method and parameters used to estimate inhalation and dermal exposures to docusate sodium from cosmetics are available in Appendix C-3.

Table 7-12. Estimated inhalation and dermal exposures to docusate sodium from the use of cosmetics

Product scenario	Docusate sodium conc.[a]	Dermal exposure (mg/kg bw/day)[b]	Inhalation exposure[b] (mg/kg bw/day)
Bath oil (9–13 years)	0.3%	0.001	N/A
Face cleanser (9–13 years)	30%	0.27	N/A
Hair shampoo (2–3 years)	10%	0.62	N/A
Fragrance product: massage oil (0–5 months)	0.3%	0.86	N/A

Product scenario	Docusate sodium conc.[a]	Dermal exposure (mg/kg bw/day)[b]	Inhalation exposure[b] (mg/kg bw/day)
Facial makeup (4–8 years)	10%	0.26	N/A
Makeup remover (4–8 years)	10%	1.0	N/A
Sunless tanning product (14–18 years)	1%	0.04	N/A
Hair bleach (14–18 years)	3%	1.0	N/A
Hair dye/highlight (14-18 years)	3%[d]	0.9	N/A
Hair styling product: aerosol (4–8 years)	0.1%	0.026	1.5×10^{-4} (0.00035 mg/m^3)[c]

Abbreviations: N/A, not Applicable; conc., concentration

[a] Personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced.

[b] Assumed absorption via dermal and inhalation route is equivalent to oral absorption.

[c] Mean concentration on day of exposure.

[d] Concentration in highlighting kit (e.g., powder); mixed with solution for application.

Docusate sodium is found as non-medicinal ingredient in six natural health products in Canada. Most of the products are for oral administration, but one is for topical application. An exposure estimate was derived for the oral natural health products using a sentinel scenario based on a tablet containing 20 mg of docusate sodium as non-medicinal ingredient for the purpose of solubilizing agent taken once daily. An exposure estimate for an adult based on 20 mg docusate sodium is 0.28 mg/kg bw/day. The potential dermal exposure associated with use of the topically applied product is considered to be addressed by the dermal cosmetic exposure estimates.

Docusate sodium is found as an active ingredient in over 70 non-prescription drugs cathartic and laxative products in Canada and as a non-medicinal ingredient in over 30 prescription and/or non-prescription drugs including oral (tablet or capsule) products and topical products. An exposure estimate for oral products was derived assuming 6 mg docusate sodium per tablet (one tablet per day) for adults, resulting in an estimate of 0.08 mg/kg bw/day. The topical products were reported or estimated to contain concentrations ranging from less than 0.05% to 0.2% docusate sodium. Exposure associated with the topically applied products was considered to be addressed by the dermal cosmetic exposure estimate. Docusate sodium is also present in products considered to be disinfectant drugs as an ingredient in aerosol and wipe disinfectant products for food premises, institutions or hospitals.

Docusate sodium is used in a variety of products available to consumers that may result in exposure in the general population in Canada, including exterior house cleaners, cleaning wipes, automotive products such as tire protectant sprays, tire cleaners (foam, aerosol and trigger spray), liquid adhesives, and wood hardener products (SDS 2013c, 2014f, 2014g, 2015i, 2015j, 2017f; HPD 1993b). Table 7-13 summarizes inhalation and dermal exposure estimates for products available to consumers containing docusate sodium.

Table 7-13. Estimated exposures to docusate sodium from the use of products available to consumers

Product scenario	Docusate sodium conc.	Dose[a] (mg/kg bw/day)
Exterior house cleaner and mildew killer	10% (m/l) 0.5%[b] (appl.)	0.014 (m/l) 0.61 (appl.) 0.62 (m/l + appl.)
Cleaning wipes/wet tissues	5%	0.63
Aerosol spray tire cleaner (aerosol/foam)	10%	0.31
Liquid paste activator (wallpaper)	0.18%[c]	0.18
Wood hardener product	20%[d]	0.81

Abbreviations: conc., concentration, m/l, mix/load activities, appl., application activities.

[a] Assumed absorption via dermal route is equivalent to oral absorption.

Inhalation exposure estimated assuming breathing rate of 16.2 m^3/day (Health Canada 1998).

[b] Product contains docusate sodium at 10% solution; after mixing and loading the product is applied in a 1:20 dilution.

[c] 30% in product; product applied in a 0.6% (product: water) solution.

[d] 20% assumed concentration in product (concentration noted as proprietary on product).

Health effects assessment

Docusate sodium has been reviewed in the US EPA screening-level hazard characterization of the sulfosuccinates category (US EPA 2009), and this review was used to inform the health effects characterization in this assessment.

A literature search was conducted from the year prior to the US EPA assessment (January 2009) to December 2020. No additional health effects studies that could result in a different health effects characterization from US EPA (2009) were identified.

Repeated-dose toxicity

Three oral studies have been identified by the US EPA (2009). There were no repeated-dose studies available for docusate sodium following inhalation or dermal exposure.

A subchronic, repeated-exposure study was conducted in 21-day old male Osborne-Mendel rats. Test animals (5/dose) were administered docusate sodium in the diet at concentrations of 0%, 2%, 4% and 8% (corresponding to 0 and approximately 2000, 4000 and 8000 mg/kg bw/day, respectively) for 16 weeks. The critical effect level and corresponding hazard endpoint were identified as a LOAEL of 2000 mg/kg bw/day, the lowest dose tested, on the basis of a decrease in body weight gain and evidence of gastrointestinal irritation upon necropsy. Only one animal exposed to 4000 mg/kg bw/day survived for the duration of the study. Animals exposed to the highest dose had severe gastrointestinal symptoms and died within the first week of treatment (US EPA 2009).

Another subchronic, repeated-exposure study was conducted in rats (strain not given (12/sex/dose) administered docusate sodium in the diet at concentrations of 0%, 0.5%, 1.0% and 1.5% (corresponding to 0 and approximately 250, 500 and 750 mg/kg bw/day, respectively) for 26 weeks. The critical effect level and corresponding hazard endpoint were identified as a NOAEL of 250 mg/kg bw/day on the basis of low weight gain and hemorrhagic gastroenteritis observed in rats exposed to 500 mg/kg bw/day. Two control animals and four test animals (sex not specified) exposed to the highest dose died. Two out of the four treated dead animals had hemorrhagic gastroenteritis. No other effects on body weights, food consumption, clinical chemistry or histopathology were observed (US EPA 2009).

In the third study, Beagle dogs (4/sex/dose) were administered docusate sodium via oral tablets at doses of 0 or 30 mg/kg bw once a day, 7 days/week, for 1 year. No treatment-related effects on body weights, food consumption, clinical chemistry, hematology and urinalysis parameters or histopathology were observed at the only dose tested. No evidence of gastric irritation was noted (US EPA 2009).

Overall, it was concluded by the US EPA (2009) that repeated oral exposures to docusate sodium in rats showed localized effects/irritation on the gastrointestinal tract at 500 mg/kg bw/day and that the NOAEL for systemic toxicity was 250 mg/kg bw/day, on the basis of decrease in body weight gain observed in rats exposed to 500 mg/kg bw/day and higher.

Reproductive/developmental toxicity

One reproductive and two developmental toxicity studies have been identified by the US EPA (2009). There are no reproductive/developmental toxicity studies available for docusate sodium following inhalation or dermal exposure.

An oral three-generation reproductive toxicity study was identified by the US EPA (2009) for docusate sodium. In this study, male and female Crl:CD(SD)BR rats were administered the substance in the diet at concentrations of 0, 0.1, 0.5 and 1% (corresponding to approximately 0, 100, 500 and 1000 mg/kg bw/day, respectively) during premating, mating and during gestation for three generations (F0, F1, F2) until weaning of the third generation (F3). The critical effect level identified in this study was a NOAEL of 100 mg/kg bw/day for both systemic and reproductive/developmental toxicity. Decreased food consumption and body weights were noted in adult animals at 500 mg/kg bw/day and higher. Male and female pups (all three generations) born to animals treated with 500 mg/kg bw/day or 1000 mg/kg bw/day weighed less than controls on day 21. An effect on lactation was also noted in animals treated with 500 mg/kg bw/day and higher; no milk was found in the abdomens on lactation day 4 in 3 control F2 pups, 7 F2 pups in the 100 mg/kg bw/day dose group, 18 F2 pups and 1 F3 pup in the 500 mg/kg bw/day dose group, and 10 F2 pups and 17 F3 pups in the 1000 mg/kg bw/day dose group. There were no treatment-related effects on the total number of pups or litters, litter size, sex ratio, or perinatal pup survival across the three generations. There were also no treatment-related mortality or microscopic observations in any animals examined (F0, F1 and F2 adults and F3 weanlings) (US EPA 2009).

In a developmental toxicity study, groups of pregnant rats were administered docusate sodium in the diet at concentrations of 0%, 1%, and 2% (corresponding to approximately 0, 500, and 1000 mg/kg bw/day, respectively) on GD 6 to GD 15. The NOAEL for maternal and developmental toxicity identified by the US EPA was 500 mg/kg bw/day, on the basis of reduction in body weight gains in dams and a significant increase in fetal resorptions and percentage of externally malformed fetuses at 1000 mg/kg bw/day. The abnormalities consisted primarily of exencephaly of varying degrees of severity. Incomplete ossification of various cranial bones and curved or open vertebral columns were also observed (US EPA 2009). In a second study, pregnant rats were exposed to docusate sodium in the diet at concentrations of 0% and 2% (corresponding to approximately 0 mg/kg bw/day and 1000 mg/kg bw/day) on GD 6 to GD 16. The LOAEL for maternal and developmental toxicity identified by the US EPA was 1000 mg/kg bw/day, the only dose tested. This LOAEL was based on decreases in maternal body weight, food intake and body weight gain, decreases in fetal body weights and crown-rump length, and increases in skeletal anomalies (unossified sternebrae) (US EPA 2009).

Repeated oral exposure to docusate sodium in rats was associated with developmental effects, such as reduced fetal and pups body weights, resorptions, malformations and skeletal anomalies, observed at 500 mg/kg bw/day or 1000 mg/kg bw/day, but only in the presence of maternal toxicity.

Genotoxicity

Docusate sodium was not mutagenic in bacterial cells nor did it induce chromosomal aberrations in mammalian cells *in vitro* (US EPA 2009).

Carcinogenicity

Docusate sodium did not show carcinogenic potential in rats (US EPA 2009). In a chronic study, male Osborne-Mendel rats (12/dose) were administered 0.25%, 0.5% or 1.0% docusate sodium in the diet for 2 years. No effect of the test substance on food intake was observed. A significant decrease in weight gain was noted in test animals exposed to 1% docusate sodium. No other treatment-related effects were observed (US EPA 2009).

Characterization of risk

Docusate sodium has been reviewed in the US EPA screening–level hazard characterization of the sulfosuccinates category (US EPA 2009), and this review was used to inform the health effects characterization in this assessment. No evidence for carcinogenicity or genotoxicity was identified in the available empirical data for this substance.

Following subchronic oral exposures to docusate sodium, site-of-contact effects on the gastrointestinal tract and decrease in body weight gain were observed in rats from 500 mg/kg bw/day. Repeated oral exposure to docusate sodium in rats was associated with developmental effects, such as reduced fetal and pups body weights, resorptions, malformations and skeletal anomalies, all of which were observed in presence of maternal toxicity.

The critical effect level identified was a NOAEL of 100 mg/kg bw/day based on systemic and reproductive/developmental toxicity in an oral three-generation reproductive toxicity study. Decreased food consumption and body weights were noted in adult animals at 500 mg/kg bw/day and higher. Male and female pups (all three generations) born to animals treated with 500 mg/kg bw/day or 1000 mg/kg bw/day weighed less than controls. An effect on lactation (no milk found in the abdomens) was also noted in animals treated with 500 mg/kg bw/day and higher (US EPA 2009)

The predominant route of exposure to docusate sodium from environmental media and food for the general population is through the diet, based on its use as a permitted food additive.

The general population of Canada may also be exposed to docusate sodium when using various products containing the substance including cleansers, hair conditioners, massage oil, makeup, body moisturizer, sunless tanning products, hair bleach, nail polish, hair styling product, various cleaning products (outdoor liquid house cleaner, trigger spray cleaners, automotive tire cleaners), wallpaper paste activator and hardener products. Exposure to docusate sodium from use of these products is expected to be primarily via the dermal route. Table 7-14 provides the relevant exposure estimates, critical health effects levels and resultant MOEs for characterization of the risk to human health from exposure to docusate sodium.

Table 7-14. Relevant exposure estimates, critical heath effects levels and resultant margins of exposure for docusate sodium

Exposure scenario	Total exposure[a] (mg/kg bw/day)	MOE based on an oral NOAEL of 100 mg/kg bw/day[b]
Total exposure from environmental media and use as a permitted food additive (oral chronic; 2–3 years)	0.338	296
Oral exposure associated with its use as a non-medicinal ingredient in prescription and/or non-prescription drugs, or	0.28	357

Exposure scenario	Total exposure[a] (mg/kg bw/day)	MOE based on an oral NOAEL of 100 mg/kg bw/day[b]
natural health product (19+ years)		
Bath oil (9–13 years)	0.001	100 000
Facial cleanser (9–13 years) (dermal chronic)	0.27	370
Hair shampoo (2–3 years) (dermal chronic)	0.62	161
Massage oil (0–5 months) (dermal intermittent)	0.86	116
Facial makeup (4–8 years) (dermal chronic)	0.26	384
Makeup remover (4–8 years)	1.0	100
Sunless tanning product (14-18 years) (dermal intermittent)	0.04	2500
Hair bleach (14–18 years) (dermal intermittent)	1.0	100
Hair dye (14–18 years) (dermal intermittent)	0.9	111
Hair styling product (4–8 years) (dermal chronic)	0.026	4 545
Exterior house cleaner (19+ years) (dermal intermittent)	0.62	161
Cleaning wipes (19+ years) (dermal chronic)	0.63	159
Aerosol spray tire cleaner (automotive) (19+ years) (dermal intermittent)	0.31	322
Wallpaper: Liquid paste activator (19+ years) (dermal intermittent)	0.18	555
Wood hardener product (19+ years) (dermal intermittent)	0.81	123

Abbreviations: MOE, margin of exposure; NOAEL, no-observed-adverse-effect level

[a] Based on the assumption that dermal absorption is equivalent to oral absorption.

[b] Systemic and reproductive/developmental toxicity in an oral three-generation reproductive toxicity study (US EPA 2009).

Overall, the MOEs are considered adequate to account for uncertainties in the health effects and exposure datasets.

7.5 Uncertainties in evaluation of risk to human health

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

Table 7-15. Sources of uncertainty in the risk characterization

Key source of uncertainty	Impact
Exposure	
In the case of methyl acetate, exposure from natural occurrence in food is based on data found in the Volatile Compounds in Food database. It was assumed that measured amounts of substance released from food are consumed.	+
For aerosol applications, instantaneous release models were used as a conservative approach.	+
Uncertainties associated with the estimate of children's exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in plastic products include the use of migration data based on saliva simulant, relevance of migration data for baby bottles in Canada, and variability in surface areas and time in contact with object.	+/-
It was assumed that dermal penetration is equivalent to oral absorption for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate and docusate sodium.	+
Hazard	
Limited hazard datasets for methyl acetate, dimethyl glutarate, and 2-methoxypropyl acetate.	+/-
There is no or limited information on repeated-dose effects via some of the relevant routes of exposure and durations, for methyl hexanoate, propyl acetate, isobutyl acetate, methyl butanoate, tetradecyl tetradecanoate, and C14-22 monoglycerides.	+/-
Lack of chronic/carcinogenicity study for methyl acetate, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, 2-methoxypropyl acetate, triacetin, C14-22 monoglycerides, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, and docusate sodium.	+/-
There is uncertainty associated with the use of available toxicological information for metabolites and analogues to characterize risk of methyl acetate, methyl hexanoate, propyl acetate, isobutyl acetate, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, and 2-methoxypropyl acetate to human health.	+/-

+ = 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.

8. Conclusion

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from the 14 substances in the Esters Group. It is proposed to conclude that methyl acetate, triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, docusate sodium, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, C14-22 monoglycerides, and 2-methoxypropyl acetate do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Considering all the information presented in this draft screening assessment, it is proposed to conclude that methyl acetate meets the criteria under paragraph 64(*c*) of CEPA as it is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Considering all the information presented in this draft screening assessment, it is proposed to conclude that triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, docusate sodium, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, C14-22 monoglycerides, and 2-methoxypropyl acetate do not meet the criteria under paragraph 64(*c*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore proposed to conclude that methyl acetate meets one or more of the criteria set out in section 64 of CEPA.

It is therefore proposed to conclude that triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, docusate sodium, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, C14-22 monoglycerides, and 2-methoxypropyl acetate do not meet any of the criteria set out in section 64 of CEPA.

It is also proposed that methyl acetate meets the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

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Appendix A. Physical-chemical property values for analogues of substances in the Esters Group

Table A-1. Physical-chemical property values for analogues

Common name (CAS RN)	MW (g/mol)	Vapour pressure (mm Hg)	Water solubility (mg/L)	log K_{ow} (dimensionless)	Used to inform the assessment of
Methyl dodecanoate (111-62-6)	214.3464	0.00411	1.13	5.41	Methyl hexanoate Methyl butanoate
Ethyl acetate (141-78-6)	116.159	11.5	8400	1.78	Propyl acetate
N-butyl acetate (123-86-4)	60.0952	21	1.00E+06	0.25	Propyl acetate
Dibasic esters (DBE/DME) Dimethyl adipate (627-93-0)	174.195	-	6000	1.03	Dimethyl glutarate
Dibasic esters (DBE/DME) Dimethyl succinate (106-65-0)	146.141	0.422	2.50E+04	0.35	Dimethyl glutarate
Propylheptyl caprylate (868839-23-0)	284.4804	-	0.004287	-	Tetradecyl tetradecanoate
Ethylhexyl laurate (20292-08-4)	312.534	3.16E-05	1.44E-03	8.03	Tetradecyl tetradecanoate
Isodecyl laurate (94247-10-6)	340.5876	-	4.21E-05	-	Tetradecyl tetradecanoate
Isopropyl myristate (110-27-0)	270.4536	3.29E-04	0.0014	7.17	Tetradecyl tetradecanoate
Isodecyl oleate (59231-34-4)	422.733	-	6.13E-08	12.759	Tetradecyl tetradecanoate
Tetradecyl oleate (22393-85-7)	478.84	3.44E-10	4.93E-10	14.4	Tetradecyl tetradecanoate
Behenyl behenate (17671-27-1)	649.177	1.21E-13	2.34E-16	21.96	Tetradecyl tetradecanoate
2-Ethylhexyl stearate (22047-49-0)	396.6948	-	4.02E-07	11.994	Tetradecyl tetradecanoate
2-Methoxypropanoic acid (4324-37-2)	104.104	1.17	4.72E+05	-0.26	2-Methoxypropyl acetate

Abbreviations: MW, molecular weight; K_{ow}, octanol–water partition coefficient

Appendix B. Estimates of daily intake from environmental media and food

Table B-1. Estimates of daily intake (µg/kg bw/day) of methyl acetate

Age categories	Ambient air[a]	Indoor air[b]	Drinking water[c]	Food and beverages[d]	Total intake
0 to 5 months[e] (breast milk-fed)[f]	0.04	5.91	N/A	0.00	5.95
0 to 5 months[e] (formula fed)[g]	0.04	5.91	10.4	0.00	16.4
6 to 11 months[h]	0.04	5.97	6.7	28.1	40.8
1 year[i]	0.05	7.32	2.6	33.1	43.1
2 to 3 years[j]	0.04	6.17	2.3	28.3	36.8
4 to 8 years[k]	0.03	4.86	1.8	21.9	28.6
9 to 13 years[l]	0.02	3.33	1.4	15.0	19.8
14 to 18 years[m]	0.02	2.58	1.4	11.2	15.2
Greater than or equal to 19 years[n]	0.01	2.05	1.7	12.1	15.85

Abbreviations: N/A, not applicable.

[a] Ambient air exposure estimates based on 95th percentile value of methyl acetate (0.57 µg/m^3) measured in Edmonton study (Health Canada 2013a). Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

[b] Indoor air exposure estimates based on 95th percentile of indoor air concentration data (11.5 µg/m^3) measured in Windsor air study (Health Canada 2010a). Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998).

[c] Concentrations in surface water were estimated with an in-house drinking water model (industrial release scenario) (Health Canada 2015a); an estimated value for surface water was found to be 79.7 µg/L and was used for deriving estimates of daily intake from drinking water exposure.

[d] Estimates of 90th percentile dietary exposure of the general population based on natural occurrence of methyl acetate in foods are presented. Food data based on concentrations reported in the Volatile Compounds in Food database (Njissen et al. 1963-2016). Food consumption rates are described in Health Canada (2015).

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

[f] Exclusively for breast milk-fed infants, assumed to consume 0.744 L of breast milk per day (Health Canada 2018), and breast milk is assumed to be the only dietary source. No breast milk monitoring data for methyl acetate were identified.

[g] Exclusively for formula-fed infants, assumed to drink 0.826 L of water per day (Health Canada 2018), where water is used to reconstitute formula. No monitoring data on methyl acetate in formula were identified. Therefore, dietary intakes are only those from water. See footnote on drinking water for details.

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

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

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

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

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

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

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

Table B-2. Estimates of daily intake (µg/kg bw/day) of 2-methoxypropyl acetate

Age categories	Ambient air[a]	Indoor air[b]	Drinking water[c]	Soil[d]	Total intake
0 to 5 months[e](breast milk-fed)[f]	0.34	0.01	N/A	N/A	0.35
0 to 5 months[e] (formula fed)[g]	0.34	0.01	0.004	N/A	0.39
6 to 11 months[h]	0.34	0.01	0.03	1.4E-6	0.38
1 year[i]	0.42	0.01	0.01	1.4E-6	0.44
2 to 3 years[j]	0.35	0.01	9.17E-3	7.4E-7	0.37
4 to 8 years[k]	0.28	8.23E-3	7.37E-3	6.81E-7	0.29
9 to 13 years[l]	0.19	5.68E-3	5.64E-3	2.96E-7	0.20
14 to 18 years[m]	0.15	4.40E-3	5.63E-3	4.1E-8	0.16
Greater than or equal to 19 years[n]	0.12	3.50E-3	6.62E-3	3.89E-8	0.13

Abbreviations: N/A, not applicable

[a] Based on SCREEN3 results, an ambient air concentration (4.61 µg/m^3) was used as a conservative approach for deriving estimates of daily exposure from ambient air. Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

[b] No Canadian indoor or ambient air monitoring data were identified. Therefore, ChemCAN results for air concentration data (1.96 ng/m^3) was used as a conservative approach for deriving estimates of daily exposure from ambient and indoor air. Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998).

[c] No Canadian water monitoring data were identified. Therefore, ChemCAN results for water concentration (0.032 µg/L) was used to derive estimates of daily intake from drinking water.

[d] No Canadian soil monitoring data were identified. Therefore, ChemCAN results for soil concentration (0.18 ng/g) was used to derive estimates of daily intake from soil.

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

[f] Exclusively for breast milk-fed infants, assumed to consume 0.744 L of breast milk per day (Health Canada 2018), and breast milk is assumed to be the only dietary source. No breast milk monitoring data for 2-methoxypropyl acetate were identified.

[g] Exclusively for formula-fed infants, assumed to drink 0.826 L of water per day (Health Canada 2018), where water is used to reconstitute formula. No monitoring data on 2-methoxypropyl acetate in formula were identified; therefore, dietary intakes are only those from water. See footnote on drinking water for details.

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

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

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

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

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

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

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

per day (Wilson and Meridian 2015 [modified]).

Table B-3. Estimates of daily intake (µg/kg bw/day) of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate

Age categories	Ambient air[a]	Indoor air[b]	Dust[c]	Total intake
0 to 5 months[d] (breast milk-fed)[e]	14.7	103.0	2.45	120.2
0 to 5 months[d] (formula fed)[f]	14.7	103.0	2.45	120.2
6 to 11 months[g]	14.9	104.1	2.12	121.1
1 year[h]	18.2	127.6	2.28	148.1
2 to 3 years[i]	15.4	107.6	1.02	124.0
4 to 8 years[j]	12.1	84.7	0.76	97.5
9 to 13 years[k]	8.29	58.1	0.41	66.8
14 to 18 years[l]	6.43	45.0	0.02	51.4
Greater than or equal to 19 years[m]	5.11	35.8	0.03	40.9

[a] No Canadian indoor or ambient air monitoring data were identified; maximum ambient air concentration from Canadian indoor air (200.5 µg/m^3) (Won and Lusztyk 2011) was used to derive an estimate of daily exposure from ambient air. Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

[b] Indoor air concentration based on the highest concentration in indoor air samples measured in Quebec City (200.5 µg/m^3) (Won and Lusztyk 2011). Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998).

[c] Maximum value of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in Canadian house dust (715 (µg/g) from Quebec City used to derive daily exposure from dust (Won and Lusztyk 2011).

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

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

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

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

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

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

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

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

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

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

Table B-4. Estimates of daily intake (μg/kg bw/day) of docusate sodium

Age categories	Drinking water[a]	Food and beverages[b]	Total intake
0 to 5 months[c] (breast milk-fed)[d]	N/A	N/A	N/A
0 to 5 months[c] (formula fed)[e]	0.07	N/A	0.07
6 to 11 months[f]	0.05	0	0.05
1 year[g]	0.02	270.7	270.7
2 to 3 years[h]	0.02	337.5	337.5
4 to 8 years[i]	0.01	274.5	274.5
9 to 13 years[j]	9.9E-3	210.0	210.0
14 to 18 years[k]	9.9E-3	134.2	134.2
Greater than or equal to 19 years[l]	0.01	58.6	58.6

Abbreviations: N/A, not applicable

[a] No Canadian water monitoring data were identified; therefore, NSACB EAU Drinking Water Spreadsheet water concentration (0.56 μg/L) was used to derive estimates of daily intake from drinking water.

[b] Food values obtained from Food Directorate and represent the 95th percentile values for each age group based on consumption of sausages and fruit drinks assuming docusate sodium found at the maximum permitted level (as a Permitted Food Additive). Food consumption rates are described in Health Canada (2015)

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

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

[e] Exclusively for formula-fed infants, assumed to drink 0.826 L of water per day (Health Canada 2018), where water is used to reconstitute formula. No monitoring data on docusate sodium in formula were identified; therefore, dietary intakes are only those from water. See footnote on drinking water for details.

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

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

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

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

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

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

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

2011 [modified]), to drink 1.53 L of water per day (Health Canada 2017), to ingest 1.6 mg of soil per day, and to ingest 2.6 mg of dust per day (Wilson and Meridian 2015 [modified]).

Appendix C. Exposure parameters

Appendix C-1. Estimates of daily intake of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate for infants from baby bottles

Concentrations of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in simulated formula were associated with the use of baby bottles (Onghena et al. 2016; Simoneau et al. 2012). While new baby bottles may be introduced at any time during infancy, a scenario was developed for early infancy (i.e., 0-1 month of age) as a conservative approach by assuming (1) that concentrations of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in formula would be observed up to the highest average reported in the literature (348 µg/kg) based on the third migration of bottles at 70°C for 2 hours (Onghena et al. 2016) and (2) that this age group would be strictly bottle-fed.

Table C-1. Intake estimates for infants associated with 2,2,4-trimethyl-1,3-pentanediol diisobutyrate migration from baby bottles

Infant age group	BW (kg)	Max. conc. (µg/kg)	Average ingestion rate (kg/day)	Max ingestion rate (kg/day)	Lower intake (max conc. + average ingestion) (µg/kg bw/day)	Upper intake (max. conc. + max. ingestion) (µg/kg bw/day)
0 to 1 month	3.9[a]	348[b]	0.644[c]	1.08[c]	57.5	96.4

Abbreviations: BW, body weight; Max., maximum; Conc., concentration

[a] Based on average female infant weight of 3.9 kg (NCHS 2000)

[b] Migration value based on conventional testing in a silicone baby bottle reported in Onghena et al. (2016). Simoneau et al. 2012 was considered a screening study and examined early migrations from baby bottles

[c] Average formula intake of 644 g/day and maximum formula intake of 1080 g/day (INSPQ 2001)

Appendix C-2. Estimates of daily intake for children aged 6 to 11 months from mouthing and dermal exposure to of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in plastic toys for children aged 6 months to 4 years

Migration rates of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from plastic toys in simulated saliva were used to estimate exposure to children mouthing toys and dermal exposure to plastic toys (Babich 2010). Migration rate data from RIVM and ANSES were also considered. However, the maximum average value from CPSC was used in the assessment (VWA 2009, as cited by Janssen and Bremmer 2009; ANSES 2016).

The parameters and intake estimates for oral exposure from mouthing as well as total potential exposure from dermal or hand-to-mouth contact are outlined in Table C-2.

Mouthing/Oral Exposure: A child with a body weight of 9.1 kg (aged 6 to 11 months) was assumed to mouth a toy for 1 to 2 hours per day (average/worst case).

Dermal and hand-to-mouth exposure: A child with a body weight of 11 kg (aged 1 year) was assumed to have dermal contact with a surface of 100 cm^2 of a toy for 3 hours per day. As no data on dermal absorption of 2,4-trimethyl-1,3-pentanediol diisobutyrate were available, it was assumed that all substance deposited on the skin would be absorbed; this assumption would also account for potential exposure through hand-to-mouth activity.

Table C-2. Intake estimates for children associated with 2,2,4-trimethyl-1,3-pentanediol diisobutyrate migration from plastic toys

Age group	BW (kg)	Migration (µg/min × 10 cm^2)	Time spent mouthing/ contacting (min/day)	Area mouthed/ touched (cm^2)	Intake (µg/kg bw/day)
6–11 months	9.1	11.3[a]	60 - 120	10	74 - 149
1 year	11	11.3[a]	180	100	1849

Abbreviation: BW, body weight

[a] US CPSC (2010)

Appendix C-3. Parameters for estimating exposure to products available to consumers

Exposure to products was estimated using ConsExpo Web (2016).

Cosmetic exposures were estimated using ConsExpo Web (2016) combined with specific parameters obtained from published literature. Exposure estimates were calculated based on default body weights of 74 kg for adults (19 years and older), 62 kg for 14- to 18-year-olds, 42 kg for 9- to 13-year-olds,15 kg for 2- to 3-year-olds, 11 kg for 1-year-olds, 9.1 kg for 6- to 11-month-olds, and 6.3 kg for 0 to 5-month-olds (Health Canada 2015). The estimated inhalation and dermal exposure parameters for cosmetics and other products available to consumers are described in Table C-3. Unless specified otherwise, the parameter values are taken from relevant ConsExpo Fact Sheet for the scenario presented.

Table C-3. Dermal and inhalation exposure parameter assumptions for esters

Exposure scenario	Assumptions
Cosmetic scenarios	
Exfoliant (mechanical) (teen/adult)	Frequency of use: 0.29 application per day (adult/teen) (Ficheux et al. 2015) Product amount: 3.1 g/application (adult/teen) (Ficheux et al. 2016) Retention factor: 0.1
Nail polish (2-3 years/adult) (methyl acetate, 2-methoxypropyl acetate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, docusate sodium) Assumes 2 coats of nail polish applied to fingernails and toenails.	From Cosmetic Fact Sheet (RIVM 2007b), with additional information on amount applied and surface area; evaporation model since substances are volatile Exposure duration: 35 minutes Product amount: 0.27 g (2-3 years); 0.8 g (adults) Room volume: 1 m^3 Weight fraction of substance: 30% (methyl acetate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate); 0.05% (2-methoxypropyl acetate) Ventilation rate: 1 hr^{-1} Mass transfer coefficient: 10 m/h (default) Release area mode: constant Release area: 8.8 cm^2 (2-3 years), 26.2 cm^2 (adult) Emission duration: 35 minutes Molecular weight matrix: 124 g/mol Dermal:

Exposure scenario	Assumptions
	Amount on skin: 0.16 g/use (adult); 0.06 g/use (2-3 years) (modified from Ficheux et al. 2014, adjusted by a factor of 0.206 for adults and 0.205 for children to account for how much nail polish ends up on skin)
Nail polish remover (2-3 years/9-13 year old; adult) (methyl acetate, methyl hexanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate)	From Cosmetic Fact Sheet (RIVM 2007b), with additional information on amount applied and surface area; evaporation model since substances are volatile Inhalation: Exposure duration: 8 minutes Product amount: 1.82 g (2–3 years); 5.36 g (adult) Room volume: 1 m^3 Ventilation rate:1 hr^{-1} Mass transfer coefficient: 10 m/h (default) Release area mode: constant Release area: 11.6 cm^2 (2–3 years); 34 cm^2 (adult) Emission duration: 5 minutes Molecular weight matrix: 75 g/mol Dermal: Amount on skin: 2.25 g/use (9–13 year old; adult); 0.76 g/use (4–8 and 2–3 years) (modified from Ficheux et al. 2014, adjusted by a factor of 0.42 (Bremmer et al. 2006) to account for how much nail polish remover is in contact with skin).
Eye adhesive (based on mascara) (adult/child) (2,2,4-trimethyl-1,3-pentanediol diisobutyrate)	Frequency of use: 1 per day (adult/14–18 yrs/9–13 yrs) (Ficheux et al. 2015) Product amount: 0.018 g/application (adult/14–18 yrs/9–13 yrs/4–8 yrs) (Ficheux et al. 2016) Retention factor: 1
Bath oil (adult/teen) (docusate sodium)	Product amount: 15 g/application (adult/14–18 yrs/9–13 yrs) (CTFA 1983) Retention factor: 0.001 (NICNAS 2009)
Facial cleanser (child/adult) (docusate sodium)	Frequency of use: 1.6 application per day (adult) (Loretz et al. 2008) 1.2 per day (14–18 yrs/9–13 yrs) (Ficheux et al. 2015) Product amount:

Exposure scenario	Assumptions
	3.3 g/application (adult/14–18 yrs) (Ficheux et al. 2016) 3.1 g/application (9–13 yrs) (surface area adjustment factor to Ficheux et al. 2016) Retention factor: 0.01
Hair conditioner: rinse out (2–3 years/adult) (docusate sodium)	Frequency of use: 1.1 application per day (adult) (Loretz et al. 2008); assumed to be 1 application per day for all other age groups Product amount: 13.1 g/application (adult) (Loretz et al. 2008) 10 g/application (14–18 yrs) (Ficheux et al. 2016) 7.8 g/application (9–13 yrs/4–8 yrs) (Ficheux et al. 2016) 5.2 g/application (2–3 yrs) (Garcia-Hidalgo et al. 2017) Retention factor: 0.01
Fragrance product: massage oil (infant/adult) (docusate sodium)	Product amount: 3.2 g/application (adult) (Ficheux et al. 2016) 1.8 g/application (0–5 months) (Ficheux et al. 2016)
Facial makeup powder (teen/adult) (docusate sodium)	Frequency of use: 1.0 application per day (adult/14–18 yrs) (Ficheux et al. 2015) Product amount: 0.073 g/application (adult/14–18 yrs) (Ficheux et al. 2016) 0.069 g/application (9–13 yrs) (surface area adjustment factor to Ficheux et al. 2016) 0.06 g/application (4–8 yrs) surface area adjustment factor to Ficheux et al. 2016)
Sunless tanning product (docusate sodium)	Product amount: 2.7 g/application (adult) (Ficheux et al. 2016). Retention factor: 0.1 (product is applied and rinsed in shower; used face mask/face exfoliation as example of retention factor)
Hair bleach (teen/adult) (docusate sodium)	Product amount: 200 g/application (adult/14–18 yrs) (Bremmer 2006) Retention factor: 0.01
Hair dye/highlight (14–18 years) (docusate sodium)	Product amount:

Exposure scenario	Assumptions
	106 g/application hair dye (adult/14–18 yrs) (Ficheux et al. 2015); assumed 50% of application amount (for highlight product instead of hair dye) Retention factor: 0.1
Hair styling product (aerosol) (docusate sodium)	Scenario: aerosol hair spray – exposure to spray Spray duration: 0.24 minute Exposure duration: 5 minutes Mass generation rate of: 0.4 g/s Room volume: 10 m^3 Weight fraction of substance: 0.3% Ventilation rate: 2 hr^{-1} Spray toward person Cloud volume: 0.0625 m^3 Airborne fraction: 0.2 Density non-volatile: 1.5 g/cm^3 Inhalation cut-off diameter: 15 μm Aerosol diameter distribution: lognormal Median diameter: 46.5 μm Arithmetic coefficient of variation: 2.1 Dermal: Product amount: 2.6 g/application (adult) (Loretz et al. 2006) 2.3 g/application (14–18 yrs; 9–13yrs; 4–8 yrs) (Ficheux et al. 2016) Retention factor: 0.09
Other products available to consumers	
Aerosol cleaner/polish; stainless steel kitchen cleaner; (methyl acetate)	Scenario: cleaning spray scenario from Cleaning Product Fact Sheet (RIVM 2007b), but used exposure to vapour – evaporation model since substances are volatile Exposure duration: 60 minutes Product amount: 7.32 g = mass generation rate of: 0.4 g/s (based on shoe polish spray rate); area of front of fridge: = 160 cm * 80 cm = 12800 cm^2 = 1.28 m^2; (Weerdesteijn et al. 1999) 14.3 s/m^2 * 1.28 m^2 = 18.3 s 0.4 g/s * 18.3 s = 7.32 g. Room volume: 15 m^3 (kitchen) Weight fraction of substance: 13%

Exposure scenario	Assumptions
	Ventilation rate: 2.5 hr^{-1} (kitchen) Mass transfer coefficient: 10 m/h (default) Release area mode: constant Release area: 1.28 m^2 Application duration: 10 minutes (includes spray, leaving on time, cleaning time) Molecular weight matrix: 120 g/mol (based on the compound of interest is not the main solvent)
Aerosol automotive spray paint (e.g., tire rims); (methyl acetate)	Scenario: spray can scenario from Paint Fact Sheet (RIVM 2007b), exposure to vapour – instantaneous release Exposure duration: 60 minutes Product amount: 545 g 2 cans at 354 mL can; density = 0.77 g/mL; assuming one can = **272.6 g** product Room volume: 90 m^3 (garage; changed ConsExpo default of 34 m^3 to 90 m^3 as estimate of two car garage (90 m^3 is the default garage volume used in US EPA Consumer Exposure Model v. 2.0 and consistent with values in Batterman et al. (2007); this garage size allows sufficient space to work on automobile) Weight fraction of substance: 26% Ventilation rate: 1.5 hr^{-1} (garage)
Aerosol tire cleaner (automotive); (methyl acetate)	Scenario: aerosol spray scenario from cleaning products Fact Sheet (RIVM 2007b); evaporation model for volatile substances; assumed spraying, leaving on and wiping down four tires. Exposure duration: 60 minutes Product amount: 16 g = mass generation rate of: 0.4 g/s (based on shoe polish spray); 0.6 min or 40 s of spraying (assuming 10 s per tire) = 40 s * 0.4g/s= **16 g product** Room volume: 34 m^3 (ConsExpo Web value for garage) Weight fraction of substance: 60% Ventilation rate:1.5 hr^{-1} (garage) Mass transfer coefficient: 10 m/h (default) Release area mode: constant Release area: 2 m^2 Emission duration: 10 minutes (from all-purpose spray cleaner)

Exposure scenario	Assumptions
	Molecular weight matrix: 200 g/mol (based on product being mainly methyl acetate)
Trigger spray tire cleaner (automotive); (methyl acetate)	Scenario: all-purpose spray scenario from cleaning products Fact Sheet (RIVM 2007b); evaporation model as substances are volatile; assumed spraying, leaving on and wiping down four tires. Exposure duration: 60 minutes Product amount: 19.7 g = mass generation rate of: 0.8 g/s (based on all purpose cleaner); 0.41 min of spraying (based on all-purpose spray) = 24.6s*0.8g/s= **19.68 g product** Room volume: 34 m^3 ((ConsExpo Web value for garage) Weight fraction of substance: 60% Ventilation rate: 1.5 hr^{-1} (garage) Mass transfer coefficient: 10 m/h Release area mode: constant Release area: 2 m^2 Emission duration: 10 minutes (from all-purpose spray cleaner) Molecular weight matrix: 200 g/mol (based on product being mainly methyl acetate)
Aerosol adhesive remover (automobile); (methyl acetate)	Scenario: spray can scenario from Paint Fact Sheet (RIVM 2007b). Exposure to vapour – evaporation model Scenario: assumed small area for adhesive remover (bumper sticker); Exposure duration: 10 minutes Product amount: 4 g = mass generation rate of: 0.4 g/s (based on shoe polish); 10 s of spraying (smaller than fridge area above) = 10 s × 0.4g/s = **4 g product** Room volume: 34 m^3 (ConsExpo Web value for garage) Weight fraction of substance: 80% Ventilation rate: 1.5 hr^{-1} (garage) Mass transfer coefficient: 10 m/h Release area mode: constant Release area: 25 cm ×10 cm = 250 cm^2 (estimated size of bumper sticker) Emission duration: 10 minutes Molecular weight matrix: 3000 g/mol (assuming the compound of interest is a main solvent)

Exposure scenario	Assumptions
Aerosol adhesive; (automotive/household); (methyl acetate)	Scenario: aerosol adhesive scenario from DIY products Fact Sheet (RIVM 2007b); spray model – instantaneous release (volatile substance) Exposure duration: 60 minutes Product amount: 204 g = mass generation rate of: 1.2 g/s (based on glue from spray); 170s of spraying = 170 s × 1.2 g/s = 204 g product Room volume: 34 m^3 (ConsExpo Web value for garage) Weight fraction of substance: 40% Ventilation rate: 1.5 hr^{-1} (garage)
Construction adhesives (joint assembly); (methyl acetate)	Scenario: cartridge gun or caulk gun application; based on assembly sealant scenario from DIY products Fact Sheet, Assembly sealant (RIVM 2007b); evaporation model as substances are volatile Exposure duration: 240 minutes Product amount: 150 g (based on product size) Room volume: 20 m^3 Weight fraction of substance: 5% Ventilation rate: 1.5 hr^{-1} (area under construction) Mass transfer coefficient: 10 m/h Release area mode: increasing Release area: 1.5 m^2 (from Fact sheet) Emission duration: 30 minutes Molecular weight matrix: 3000 g/mol (assuming the compound of interest is a main solvent)
Tube glue; (methyl acetate)	Scenario: tube glue (contact glue) in Do-It-Yourself Fact Sheet (tur Burg et al. 2007) Exposure duration: 30 minutes (considered appropriate for small jobs; 18 mL container) Product amount: 9 g Room volume: 20 m^3 (unspecified) Weight fraction of substance: 95%–50% Ventilation rate: 0.6 hr^{-1} Mass transfer coefficient: 10 m/h Release area mode: increasing Release area: 0.02 m^2 (from Fact sheet) Emission duration: 10 minutes Molecular weight matrix: 3000 g/mol
Aerosol lubricant (e.g., gun cleaning); (methyl acetate)	Scenario: aerosol spray scenario adapted from cleaning products Fact Sheet (RIVM 2007b) – cleaning;

Exposure scenario	Assumptions
	evaporation model; assumed spraying, leaving on and wiping down gun. Exposure duration: 60 minutes Product amount: 15 g = mass generation rate of: 1.5 g/s (based on lubricant penetrating spray); 10 s of spraying (assuming 10 s per tire) = 40 × 0.4g/s = 16 g product Room volume: 34 m^3 (ConsExpo Web value for garage) Weight fraction of substance: 10% Ventilation rate: 1.5 hr^{-1} (garage) Mass transfer coefficient: 10 m/h Release area mode: constant Release area: 1.5 m^2 (estimated) Emission duration: 10 minutes (based on all purpose spray cleaner) Molecular weight matrix: 300 g/mol (used similar approach as stainless steel cleaner)
Paint remover; (methyl acetate)	Scenario: paint remover, approach adapted from the Do-It-Yourself Fact Sheet (RIVM 2007a); exposure to vapour model with evaporation. Exposure period: 90 minutes (20 minute application; 20 minute wait (not in room; air concentrations during this time not included in estimate); 50 minute removal activity) Project type/Product amount/Release area/Room volume/ ventilation rate - Small project: 868 g (1 m^2), 34 m^3; 0.5–2.5 hr^{-1} - Large project: 7819 g (9 m^2), 34 m^3; 0.5–2.5 hr^{-1} - Bathtub: 2867 g (3.3 m^2); 10 m^3; 2 hr^{-1} - Product amounts based on application rate in technical data sheet for product (TDS 2019) Emission factor: 50% (represents amount of substance available for evaporation to account for potential presence of evaporation barriers (used in product for efficacy); based on literature indicating 10% to 30% chemical evaporated (adapted from Van Veen et al. 2002).

Exposure scenario	Assumptions
	Weight fraction of substance: 70% Mass transfer coefficient: 3.44 m/h Release area mode: increasing Application duration: 20 minutes Molecular weight matrix: 100 g/mol (estimated) Estimated mean 24-hour air concentrations are reported in Table 7-3. Peak and Event concentrations are found below: Peak concentrations: - Small project (lower/higher vent): 7960/5820 mg/m^3 - Large project (lower/higher vent): 68 900/50 700 mg/m^3 - Bathroom: 67 000 mg/m^3 Event concentration - Small project (lower/higher vent): 3893/1257 mg/m^3 - Large project (lower/higher vent): 34 453/11 384 mg/m^3 - Bathroom: 18 183 mg/m^3
Garage floor coating; (methyl acetate)	Scenario: general coating on a floor (in a garage) in Do-It-Yourself Fact Sheet (RIVM 2007a) Exposure duration: 90 minutes Product amount: 900 g (based on application rate of 1L product/30 m^2 as outlined in technical data sheet) Room volume: 34 m^3 (ConsExpo Web value for garage) Weight fraction of substance: 10% (concentration in applied product, i.e., Part A and Part B mixed) Ventilation rate: 1.5 hr^{-1} (garage); Mass transfer coefficient: 10 m/h Release area mode: increasing Release area: 25 m^2 (floor surface area matches volume and amount applied) Emission duration: 90 minutes Molecular weight matrix: 3000 g/mol (assuming the compound of interest is a main solvent)
Aerosol paint (2-methoxypropyl acetate)	Scenario: spray can scenario from Paint Fact Sheet (RIVM 2007b). Exposure to vapour – evaporation model Exposure duration: 20 minutes Product amount: 300 g Room volume: 34 m^3 (ConsExpo Web value for garage) Weight fraction of substance: 0.1% Ventilation rate: 1.5 hr^{-1} (garage) Mass transfer coefficient: 10 m/h

Exposure scenario	Assumptions
	Release area mode: constant Release area: 2 m^2 Emission duration: 15 minutes Molecular weight matrix: 300 g/mol (compound of interest is not a main solvent) Dermal: Contact rate: 100 mg/min Release duration: 15 minutes
Putty filler (2-methoxypropyl acetate)	Scenario: Large hole filler scenario in DIY products Fact Sheet (RIVM 2007b); evaporation model Exposure duration: 240 minutes Product amount: 150 g (from fact sheet) Room volume: 34 m^3 (ConsExpo Web value for garage) Weight fraction of substance: 0.1% Ventilation rate: 1.5 hr^{-1} Mass transfer coefficient: 10 m/h Release area mode: constant Release area: 200 cm^2 (from Fact sheet) Emission duration: 240 minutes Molecular weight matrix: 3000 g/mol (assuming the compound of interest is a main solvent) Dermal: Product amount: 0.5 g
Aerosol primer (2,2,4-trimethyl-1,3-pentanediol diisobutyrate) (spray model)	Scenario: spray can scenario from Paint Fact Sheet (RIVM 2007b); used exposure to spray (exposure to vapour was lower) Spray duration: 15 minutes Exposure duration: 20 minutes Weight fraction of substance: 5% Room volume: 34 m^3 (ConsExpo Web value for garage) Ventilation rate: 1.5 hr^{-1} (garage) Mass generation rate: 0.45 g/s (aerosol paint) Airborne fraction: 0.7 Density non-volatile: 1.5 g/cm^3 Inhalation cut off diameter: 15 μm Lognormal aerosol diameter distribution: median diameter of 15.1 μm; Arithmetic coefficient of variation = 1.2 Dermal: Contact rate: 100 mg/min

Exposure scenario	Assumptions
	Release duration: 15 minutes
Marine/pool paint (outdoors; only dermal) (2,2,4-trimethyl-1,3-pentanediol diisobutyrate)	Based on brush/roller paint: Dermal: Contact rate: 30 mg/min Release duration: 180 minutes
Liquid hardener; fiberglass repair kit; (2,2,4-trimethyl-1,3-pentanediol diisobutyrate)	Scenario: DIY products Fact Sheet (RIVM 2007b); evaporation model; used 2-component glue scenario Mix/load - inhalation: Exposure duration: 5 minutes Product amount: 20 g (from fact sheet) Room volume: 1 m^3 Weight fraction of substance: 30% Ventilation rate: 0.6 hr^{-1} Mass transfer coefficient: 10 m/h Release area mode: constant Release area: 0.002 m^2 (from Fact sheet) Emission duration: 5 minutes Molecular weight matrix: 3000 g/mol Mix/load - dermal: Product amount: 0.05 g Apply – inhalation: Exposure duration: 240 minutes Product amount: 20 g (from fact sheet) Room volume: 20 m^3 Weight fraction of substance: 30% Ventilation rate: 0.6 hr^{-1} Mass transfer coefficient: 10 m/h Release area mode: increasing Release area: 0.05 m^2 (from Fact sheet) Emission duration: 30 minutes Molecular weight matrix: 3000 g/mol (assuming the compound of interest is a main solvent) Dermal: Product amount: 0.1 g (100 mg)
Concrete crack repair; (2,2,4-trimethyl-1,3-pentanediol diisobutyrate)	Scenario: DIY products Fact Sheet (RIVM 2007b); filler/putty from tube evaporation model Exposure duration: 240 minutes Product amount: 40 g (from fact sheet) Room volume: 34 m^3 (ConsExpo Web value for garage)

Exposure scenario	**Assumptions**
	Weight fraction of substance: 40% Ventilation rate: 0.6 hr^{-1} Mass transfer coefficient: 10 m/h Release area mode: increasing Release area: 0.02 m^2 (from Fact sheet) Emission duration: 20 minutes Molecular weight matrix: 3000 g/mol (assuming the compound of interest is a main solvent) Dermal: Product amount: 0.05 g (50 mg)
Hobby paint; (2,2,4-trimethyl-1,3-pentanediol diisobutyrate)	Scenario of paint on slightly stained hand was approximately 50 mg. Assumed 50 mg on child's hand during hobby painting
Exterior house cleaner and mildew killer; (docusate sodium)	Scenario: algae green deposit remover from Disinfectant Products Fact Sheet (RIVM 2007b) Mix/load: Exposed area: 215 cm^2 Product amount: 0.01 g Application: Contact rate: 540 mg/min Release duration: 16.7 minutes
Trigger spray cleaner; (docusate sodium)	Scenario: trigger spray; exposure to spray Spray duration: 0.23 minutes Exposure duration: 60 minutes Weight fraction: 13.5% Room volume: 15 m^3 Ventilation rate: 2.5 hr^{-1} Mass generation rate of: 1.6 g/s Airborne fraction: 0.1 Density non-volatile: 1 g/cm^3 Inhalation cut off diameter: 15 μm Lognormal aerosol diameter distribution: median diameter of 2.4 μm; Arithmetic coefficient of variation = 0.37 Dermal (spray): Contact rate: 46 mg/min Release duration: 0.23 minutes Dermal (wipe):

Exposure scenario	Assumptions
	Product amount: 0.16 g
Cleaning wipes/wet tissues; (docusate sodium)	Scenario: Wet tissue wipes (hands) (Ficheux et al. 2016) Dermal: Product amount: 0.9 g remained on hand
Aerosol spray tire cleaner: foam (docusate sodium)	Scenario: based on elements from foam carpet spray spot remover scenario from Cleaning Products Fact Sheet (RIVM 2007b); Assumed 10 s spray/tire = 40 s Mass generation rate: 0.6 g/s (furniture spray can) = 24 g 1% available for dermal exposure (consistent with foam carpet cleaner) = 0.24 g = 240 mg product dermal exposure
Liquid paste activator (wallpaper); (docusate sodium)	Dermal: Contact rate: 30 mg/minute Release duration: 240 minutes
Wood hardener product; (docusate sodium)	Liquid brush on product: based on brush on paint product exposure contact rate. Dermal: Contact rate: 30 mg/minute Release duration: 10 minutes (based on type of product)

Appendix D. Parameters to estimate drinking water exposure

Table D-1. Human exposure parameter inputs and assumptions for releases to waste water scenarios derived with the NSACB EAU Drinking Water Spreadsheets

Substance	**Methyl acetate**	**Docusate sodium**
Scenario	Industrial release	Industrial release
Quantity at site	Section 71 total import value for substance (323,602 kg)	Section 71 total import values for substance (1,081,185 kg)
Wastewater treatment system (WWTS) removal rate (%)[a]	0	27.83
Number of industrial sites	1[b]	30
Release days (per year)[b]	250	250
Daily release to wastewater (%)	1[c]	1[d]
Receiving water body[b]	Thames River, London ON	Thames River, London ON

[a] ECCC (2016a)

[b] NSACB EAU Drinking Water Spreadsheet default

[c] Generic emission factor

[d] Based on 1% releases from handling of substance in powder form and 0% as transfer line/process vessel residues for dry substance.

Appendix E. SCREEN3: Model and inputs

SCREEN3 is a screening-level Gaussian air dispersion model based on the Industrial Source Complex (ISC) model (for assessing pollutant concentrations from various sources in an industry complex) (SCREEN3 2011). The driver for air dispersion in the SCREEN3 model is wind. The maximum calculated exposure concentration is selected based on a built-in meteorological data matrix of different combinations of meteorological conditions, including wind speed, turbulence and humidity. This model directly predicts concentrations resulting from point, area and volume source releases. SCREEN3 gives the maximum concentrations of a substance at chosen receptor heights and at various distances from a release source in the direction downwind from the prevalent wind 1 hour after a given release event. During a 24-hour period, for point emission sources, the maximum 1-hour exposure (as assessed by the ISC Version 3) is multiplied by a factor of 0.4 to account for variable wind direction. This gives an estimate of the air concentration over a 24-hour exposure (US EPA 1992; SCREEN3 2011). Similarly, for exposure events happening over the span of a year, it can be expected that the direction of the prevalent winds will be more variable and uncorrelated to the wind direction for a single event; thus, the maximum amortized exposure concentration for 1 year is determined by multiplying the maximum 1-hour exposure by a factor of 0.08 (US EPA 1992; SCREEN3 2011). The parameters used to estimate ambient air concentrations from 2-methoxypropyl acetate in air using the SCREEN3 model are presented in Table E-1 below.

Table E-1. Parameters used in SCREEN3 for air releases from industrial facilities for PMA

Parameter	Input
Source type	Area
Effective emission area[a]	150 m × 100 m
Receptor height[b]	1.74 m
Source release height[a]	5 m
Adjustment factor[c]	0.4
Urban-rural option	Rural
Meterology[d]	1 (full meterology)
Minimum and maximum distance	0-3000 m
Distance from source facility to residential areas[a]	300 m

[a] Site specific; based on aerial photograph analysis and professional judgement
[b] Average adult height (Curry et al. 1993)
[c] Factor to account for variable wind direction over a 24-hour period (US EPA 1992)
[d] Default value in SCREEN3