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Draft Screening Assessment

Terpenes and Terpenoids

Acyclic, Monocyclic, and Bicyclic Monoterpenes Group

Environment and Climate Change Canada
Health Canada

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Synopsis

Pursuant to section 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment on 15 of 76 substances referred to collectively under the Chemicals Management Plan as the Terpenes and Terpenoids Group. These 15 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. Four of the other 61 substances were subsequently determined to be of low concern for risk to ecological and human health and the decision for these substances are provided in separate reports.[1,2] Decisions on the remaining 57 substances will be communicated in several separate risk assessments. Accordingly, this screening assessment addresses the 15 substances listed in the table below, which will hereinafter be referred to as the Acyclic, Monocyclic, and Bicyclic Monoterpenes Group. The Chemical Abstracts Service Registry Numbers (CAS RN[3]), their *Domestic Substances List* (DSL) names and the substance names used in this assessment are in the table below.

Substances in the Acyclic, Monocyclic, and Bicyclic Monoterpenes Group

CAS RN	DSL name	Substance name used in this assessment
80-56-8	Bicyclo[3.1.1]hept-2-ene, 2,6,6-trimethyl-	alpha-pinene
1113-21-9	1,6,10,14-Hexadecatetraen-3-ol, 3,7,11,15-tetramethyl-, (E,E)-	geranyllinalool
8000-46-2 [a,b]	Oils, geranium	geranium oil
8002-09-3 [a]	Oils, pine	pine oil
8006-64-2 [a]	Turpentine, oil	turpentine oil
8007-01-0 [a]	Oils, rose	rose oil
8007-02-1 [a]	Oils, lemongrass	lemongrass oil
8008-31-9 [a,b]	Oils, mandarin	mandarin oil
8008-52-4 [a]	Oils, coriander	coriander oil
8008-57-9 [a]	Oils, orange, sweet	sweet orange oil
8014-19-5 [a,b]	Oils, palmarosa	palmarosa oil

[1] The conclusion for CAS RN 25428-43-7 and 4572-09-2 are provided in the Rapid Screening of Substances with Limited General Population Exposure.

[2] Conclusions for CAS RNs 29350-73-0 and 68916-97-2 are provided in the Screening Assessment: 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.

[3] 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.

8015-77-8 [a,b]	Oils, bois de rose	bois de rose oil
8016-85-1 [a,b]	Oils, tangerine	tangerine oil
8021-28-1 [a,b]	Oils, fir	fir oil
9005-90-7 [a,b]	Turpentine	turpentine

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

Terpenes have repeating isoprene units and they are grouped according to the number of isoprene units they contain. Monoterpenes are the smallest unit and contain two isoprene units. Plant derived essential oils have many components which can be extracted from different parts of a plant (e.g., leaves, seed, stem, flower, root, fruits, woods, barks, grass, gum, tree blossoms, bulbs, flower buds). The concentration of these main components can be affected by different factors such as the origin of the plant, its species, temperature, soil, and geography. In addition, many of these oils have different chemotypes (i.e. different major chemical components produced from plants with the same genus and species). Therefore, the essential oils extracted from these plants may be chemically different even though their origin is the same.

All of the substances in the Acyclic, Monocyclic, and Bicyclic Monoterpenes Group, except turpentine oil, have been included in surveys issued under section 71 of CEPA and were found to be generally used as fragrances in personal care products [4] (e.g., body lotion, shampoos, drugs and natural health products), cleaning products, and air fresheners.

The ecological risks of substances in the Acyclic, Monocyclic, and Bicyclic Monoterpenes Group were characterized using the ecological risk classification of organic substances (ERC) approach, 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 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 Acyclic, Monocyclic, and Bicyclic Monoterpenes Group are considered unlikely to be causing ecological harm.

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

Considering all available lines of evidence presented in this draft screening assessment, there is low risk to the environment from the 15 substances in the Acyclic, Monocyclic, and Bicyclic Monoterpenes Group. It is proposed to conclude that these 15 substances in the Acyclic, Monocyclic, and Bicyclic Monoterpenes Group do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Human exposure was characterized from use of personal care products, cleaning products, air fresheners containing the monoterpenes, and use as a solvent to clean paint brushes and remove paint.

With respect to human health, bois de rose oil, palmarosa oil, geranium oil, geranyllinalool and sweet orange oil demonstrated low hazard potential, and thus were assessed qualitatively. Given the low hazard potential, risk to human health is also considered to be low.

Critical health effects associated with exposure to coriander oil were kidney and liver effects as well as changes in serum biochemistry. A comparison of estimated levels of exposure to coriander oil from food and products available to consumers and critical effect levels results in margins of exposure that are considered to be adequate to address uncertainties in exposure and health effects data used to characterize risk.

For rose oil, critical health effects were significant and dose related; a decrease in hematocrit and hemoglobin values along with significant increases in spleen weights were found. A comparison of estimated levels of exposure to rose oil to infants and toddlers from a body moisturizer containing 3% rose oil and critical effect levels results in margins of exposure that are considered potentially inadequate to address uncertainties in exposure and health effects data used to characterize risk.

As there were no health effect studies available for lemongrass oil, health effects information from lemongrass extract and from citral, the main component of lemongrass oil, were used. In repeated dose studies, lemongrass extract exhibited increased levels of certain liver enzymes, as well as vascular congestion and scarring in the liver. Citral exhibited reproductive toxicity. A comparison of estimated levels of exposure to lemongrass oil from food and products available to consumers and critical effect levels results in margins of exposure that are considered adequate to address uncertainties in exposure and health effects data used to characterize risk.

No relevant toxicity data were identified for mandarin/tangerine oils and, as such, the health effects information available for their main components limonene, gamma-terpinene, and citral were considered. While limonene showed low hazard potential, one isomer of gamma-terpinene (alpha-terpinene), showed a potential to act as a developmental or reproductive toxicant. As such, the critical health effect was developmental toxicity. In addition, effects by the inhalation route were based on effects

observed in an inhalation study with citral. A comparison of estimated levels of exposure to mandarin and tangerine oil from use of a body moisturizer and dietary supplement, and critical effect levels results in margins of exposure that are considered potentially inadequate to address uncertainties in exposure and health effects data used to characterize risk.

For alpha-pinene, the critical health effects, depending on the duration of exposure, were effects on the kidney and liver, or effects on the bladder and decreased sperm cauda. Comparisons of estimated levels of exposure to alpha-pinene from food, environmental media, and products available to consumers, and critical effect levels results in margins of exposure that are considered to be adequate to address uncertainties in exposure and health effects data used to characterize risk.

For turpentine/turpentine oil, critical health effect information was based on effects observed with its main component alpha-pinene. Comparisons of estimated levels of exposure to turpentine/turpentine oil from its use as a paint thinner and remover, and its presence as a non-medicinal ingredient in a topical medicated vapour product and counterirritant product, and critical effect levels results in margins of exposure that are considered potentially inadequate to address uncertainties in exposure and health effects data used to characterize risk.

Critical health effect information for fir oil was also based on effects observed with its main component alpha-pinene. A comparison of estimated levels of exposure to fir oil from food and products available to consumers, and critical effect levels results in margins of exposure that are considered to be adequate to address uncertainties in exposure and health effects data used to characterize risk.

For pine oil, the critical health effects were reproductive toxicity and systemic toxicity. Comparisons of estimated levels of exposure to pine oil from food and products available to consumers, and critical effect levels results in margins of exposure that are considered to be adequate to address uncertainties in exposure and health effects data used to characterize risk.

For rose oil, mandarin oil, tangerine oil, turpentine oil, and turpentine, comparisons of levels at which critical health effects occur with levels Canadians may be exposed to result in margins of exposure considered potentially inadequate to address uncertainties in the health effects and exposure databases.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that bois de rose oil, palmarosa oil, geranium oil, geranyllinalool, coriander oil, lemongrass oil, sweet orange oil, alpha-pinene, fir oil and pine oil 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.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that rose oil, mandarin oil, tangerine oil, turpentine oil and turpentine meet the criteria under paragraph 64(*c*) of CEPA as they are 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.

Therefore, it is proposed to conclude that rose oil, mandarin oil, tangerine oil, turpentine oil and turpentine meet one or more of the criteria set out in section 64 of CEPA and that the remaining 10 substances in the Acyclic, Monocyclic, and Bicyclic Monoterpenes Group do not meet any of the criteria set out in section 64 of CEPA.

It is also proposed that rose oil, turpentine oil, and turpentine do not meet the persistence or bioaccumulation criteria, while mandarin and tangerine oil meet the bioaccumulation criteria but not the persistence 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 on 15 of 76 substances, referred to collectively under the Chemicals Management Plan as the Terpenes and Terpenoids Group, to determine whether these 15 substances present or may present a risk to the environment or to human health. These 15 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 2017a).

Out of the other 61 substances, four substances (listed in Table 1-1, below) were considered in the Ecological Risk Classification of Organic Substances (ERC) Science Approach Document (ECCC 2016a), and in either the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Science Approach Document (HC 2016), or via the Rapid Screening of Substances with Limited General Population Exposure (ECCC, HC 2018a), 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 two of these four 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 2018b), while proposed conclusions for the other two substances are provided in the Rapid Screening of Substances with Limited General Population Exposure Screening Assessment (ECCC, HC 2018a). Decisions on the remaining 57 substances will be communicated in several risk assessments.

Table 1-1. Substances in the Terpenes and Terpenoids Group that were addressed under other approaches

CAS RN	DSL name	Approach under which the substance was addressed	References
68916-97-2	Oils, horehound	ERC/TTC	ECCC, HC 2018b
29350-73-0	Naphthalene, decahydro-1,6-dimethyl-4-(1-methylethyl)-, [1S-(1α,4α,4aα,6α,8aβ)]-, didehydro deriv.	ERC/TTC	ECCC, HC 2018b

[5] 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	Approach under which the substance was addressed	References
4572-09-2	Olean-12-en-29-oic acid, 3-hydroxy-11-oxo-, (3β,20β)-, compd. with (2,5-dioxo-4-imidazolidinyl)urea (1:1)	ERC/Rapid Screening	ECCC, HC 2018a
25428-43-7	3-Cyclohexene-1-methanol, α,4-dimethyl-α-(4-methyl-3-pentenyl)-, (R,R)-(±)-	ERC/Rapid Screening	ECCC, HC 2018a

The 15 substances addressed in this draft screening assessment report will hereinafter be referred to as the Acyclic, Monocyclic, and Bicyclic Monoterpenes Group. The 15 substances were divided into two subgroups, the acyclic monoterpenes and the monocyclic and bicyclic monoterpenes. Within each subgroup, each substance was assessed independently due to considerable differences with respect to exposure, hazard, and risk characterization.

The ecological risks of the substances in the Acyclic, Monocyclic, and Bicyclic Monoterpenes 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 it 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.

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 June 2017. Empirical data from key studies as well as some 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 portions of this assessment have undergone external peer review and/or consultation. Comments on the technical portions relevant to human health were received from Herman Gibb, Gary Drendel and Jennifer Pitt (TetraTech Inc.). 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[6]. This draft screening assessment presents the critical information and considerations on which the proposed conclusions are based.

2. Identity of substances

The CAS RNs and DSL names for the individual substances in the Acyclic, Monocyclic and Bicyclic Monoterpenes Group and their main components in the case of UVCBs are presented in Table 2-1.

All terpenes and terpenoids are derived from the common 5-carbon building blocks isopentenyl diphosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP), also known as isoprene units (Figure 1). Terpenes are repeating isoprene units and they are classified according to the number of isoprene units they contain (Caputi & Aprea 2011). Monoterpenes contain two isoprene units. The prefixes *Di-, Tri-, or Tetra*-terpene refer to two, three, and four monoterpene units, respectively. Furthermore, sesquiterpenes and sesterpenes contain three and five isoprene units, respectively.

Figure 1: Isoprene Unit

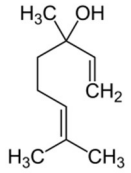
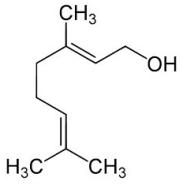
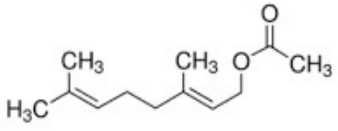
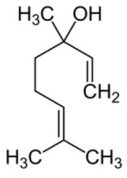
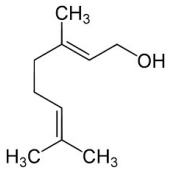
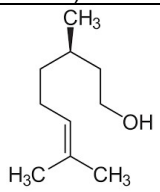
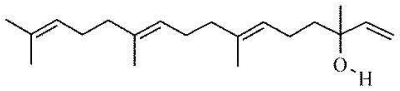
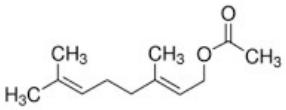
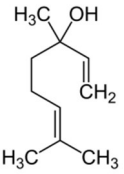
[6]A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient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

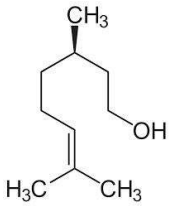
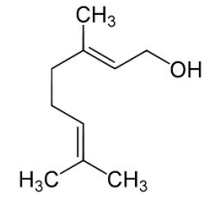
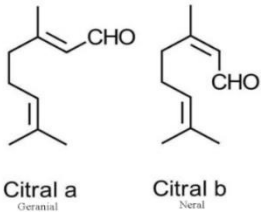
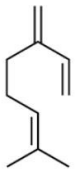
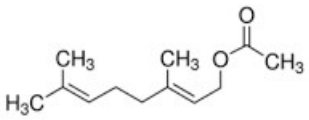
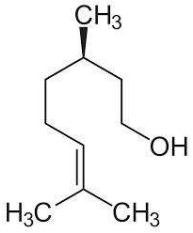
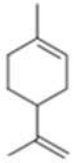
Isoprene
(2-methyl-1,3-butadiene)

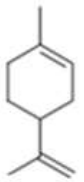
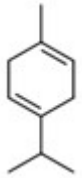
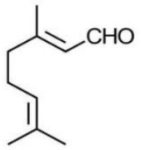
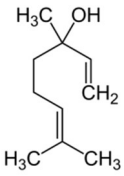
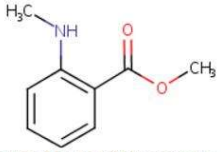
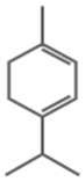
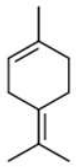
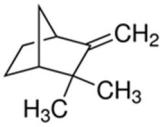
These plant derived essential oils have many components which can be extracted from different parts of a plant (e.g. leaves, seed, stem, flower, root, fruits, woods, barks, grass, gum, tree blossoms, bulbs, flower buds) (Tisserand and Young 2014). In addition, the concentration of these main components can be affected by different factors such as the origin of the plant, its species, temperature, soil, and geography. Many of these oils also have different chemotypes (i.e. different major chemical components produced from plants with the same genus and species). Therefore, the essential oils extracted from these plants are chemically different even though their origin is the same.

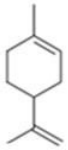
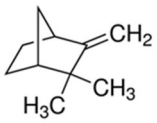
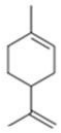
During the grouping of terpenes and terpenoids, the first criterion was placed on the number of isoprene units and a second criterion was placed on the number of cyclic parts in the “main components”. For example, one of the subgroups is known as the Acyclic Monoterpene group because their main components (linalool, geraniol, and citronellol) contain two isoprene units and no cyclic portions in their structure.

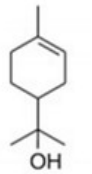
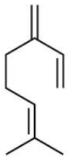
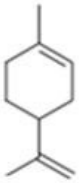
Table 2-1. Substance identity for those identified as UVCBs* and discrete substances in this assessment

CAS RN	DSL name	Representative chemical name(s), structure(s), and their range of concentration(s) in the essential oil
8015-77-8	Oils, bois de rose	 Linalool (~81-99) [a]
8014-19-5	Oils, palmarosa	 Geraniol (~70-92%) [b]  Geranyl acetate (~4-16%) [b]
8000-46-2	Oils, geranium	 Linalool (~5-14%)[c]  Geraniol (~20-30%)[c]  Citronellol (~37-48%)[c]
1113-21-9	Geranyllinalool (discrete substance)	
8008-52-4	Oils, coriander	 Geranyl acetate (~0-46%) [d]  Linalool (~59-88%)[d]  Alpha-pinene (~ 0.1-11%)[d]

8007-01-0	Oils, rose	 Citronellol (~15-48%) [e]  Geraniol (~6-32%) [e]
8007-02-1	Oils, lemongrass	 Citral a (Geranial) Citral b (Neral) Total Citral (mixture of both isomers) (~67-92%)[f]  Beta-myrcene (~6-27%)[f]  Geranyl acetate (~12%)[f]  Citronellol (~0-24%)[f]
8008-57-9	Oils, sweet, orange	 Limonene (~84-96%)[h]

8008-31-9 and 8016-85-1	Oils, mandarin and Oils, tangerine	 Limonene (~52-92%)[g]  Gamma-terpinene (~tr-61%)[g]  Citral a Geranial Citral b Neral Total Citral (mixture of both isomers) (~15-19%)[g]  Linalool (~0.2-59%)[g]  Methyl N-methylanthranilate (~0-58%)[g]  Alpha-terpinene  Delta-terpinene (alpha & delta-terpinene provided for comparison and reference only)
80-56-8	Alpha-pinene (discrete substance)	 Alpha-pinene  Camphene (provided for comparison and reference only)

8006-64-2 and 9005-90-7	Oils, turpentine and Turpentine	 Alpha-pinene (~44-94%)[i]  Beta-pinene (~0.9-30%)[i,l]  Limonene (~0.7-25%)[i]  Camphene (~1-15%)[i]
8021-28-1	Oils, fir	  Camphene (provided for comparison and reference only) Alpha-pinene (~6-26%)[j]  Beta-pinene (~28-56%)[j, l]  Limonene (~2-16%)[j]

8002-09-3	Oils, pine	 Alpha-terpineol (~0-65%)[k]  Alpha-pinene (~12-69%)[k]  Beta-pinene (~0.17-33%)[k,l]  Beta-myrcene (~0-18%)[k]  Camphene (~0.8-11%)[k]  Limonene (~0-16%)[k]

[*] UVCB is an acronym for Unknown or Variable composition Complex reaction products and Biological material. These materials are derived from natural sources or complex reactions. A UVCB is not an intentional mixture of discrete substances and is considered a single substance.

[a] Concentration range of the main component(s) for *Aniba rosaeodora*'s essential oil captured from Tisserand and Young (2014), Simić et al. (2004), and Chantraine et al. (2009).

[b] Concentration range of the main component(s) for *Cymbopogon martinii*'s essential oil captured from Tisserand and Young (2014), Sarma et al. (1998), Rajeswara et al. (2009), and Raina et al. (2003).

[c] Concentration range of the main component(s) for *Pelargonium graveolens's* essential oil captured from Tisserand and Young (2014) and Jain et al. (2001).

[d] Concentration range of the main component(s) for *Coriandrum sativum's* essential oil captured from Tisserand and Young (2014) and Ebrahimi et al. (2010).

[e] Concentration range of the main component(s) for *Rosa damascena's* essential oil captured from Tisserand and Young (2014), Loghmani-Khouzani et al. (2007), Boskabady et al. (2011), Babu et al. (2002), and Dobreva (2013).

[f] Concentration range of the main component(s) for *Cymbopogon flexuosus or Cymbopogon citratus's* essential oil captured from Tisserand and Young (2014), Chowdhury et al. (2010) and Nath et al. (1994).

[g] Concentration range of the main component(s) for *Citrus reticulate and/or Citrus nobilis's* essential oil captured from Tisserand and Young (2014), Chutia et al. (2009), Sawamura et al. (2004), Lota et al. (2000).

[h] Concentration range of the main component(s) for *Citrus sinensis's* essential oil captured from Tisserand and Young (2014), Sharma and Tripathi, (2008), Njoroge et al. (2009).

[i] Concentration range of the main component(s) of essential oil extracted from different species of plant family '*Pinaceae'* (*Pinus palustris, Pinus caribaea, Pinus eliottii, Pinus insularis, Pinus merkusii, Pinus pinaster, Pinus yunnanensi)* captured from Tisserand and Young (2014) and NTP (2002).

[j] Concentration range of the main component(s) for *Abies balsamea's* essential oil captured from Tisserand and Young (2014) and Ross et al. (1996).

[k] Concentration range of the main component(s) of essential oil extracted from different species of plant family '*Pinaceae'* (*Pinus palustris, Pinus mugo, Pinus sylvestris)* captured from Tisserand and Young (2014), US EPA (2009), Sadof (1997), Maciąg et al. (2007), Ustun et al. (2006), and Harborne and Baxter (2001).

[l] No relevant toxicity data exists for this substance

3. Physical and chemical properties

A summary of physical and chemical properties of the substances in the Acyclic, Monocyclic and Bicyclic Monoterpenes Group are presented in Table 3-1. When experimental information was limited or not available for a property, data from analogues were used for read-across and/or (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. Physical and chemical property values (at standard temperature) of discrete substances and main components of UVCBs in the Acyclic, Monocyclic, and Bicyclic Monoterpenes Group

Substance(s)	Main components common name and CAS RN:	Molecular weight (g/mol) [a]	Water solubility (mg/L) [a]	VP (Pa) [a]	Henry's law constant (atm-m^3/mol) [a]	Log Kow [a]
Oils, Bois de rose	Linalool (78-70-6)	154.25	1590(E)	21(E)	2.15 x 10^{-5} (E)	2.9(E)
Oils, Palmarosa	Geraniol (106-24-1)	154.25	255.8(M)	4(E)	1.15 x 10^{-5} (E)	3.5(E)
	Geranyl acetate (105-87-3)	196.29	18.24(M)	4.4(E)	2.42 x 10^{-3} (M)	4(E)
Oils, Geranium	Citronellol (106-22-9)	156.27	105.5(M)	5.9(E)	5.68 x 10^{-5} (M)	3.9(E)
	Geraniol (106-24-1)	154.25	255.8(M)	4(E)	1.15 x 10^{-5} (E)	3.5(E)
	Linalool (78-70-6)	154.25	1590(E)	21(E)	2.15 x 10^{-5} (E)	2.9(E)
Geranyllinalool	NA	290.49	6.98 x 10^{-3} (M)	2.07 x 10^{-4} (M)	7.75 x 10^{-4} (M)	7.97(M)
Oils, Coriander	Linalool (78-70-6)	154.25	1590(E)	21(E)	2.15 x 10^{-5} (E)	2.9(E)
	Geranyl acetate (105-87-3)	196.29	18.24(M)	4.4(E)	2.42 x 10^{-3} (M)	4(E)
	Alpha-pinene (80-56-8)	136.24	2.49 at 25°C(E)	633(E)	1.07 x 10^{-1} (M)	4.44 – 4.83 (E)
Oils, Rose	Citronellol (106-22-9)	156.27	105.5 (M)	5.9(E)	5.68 x 10^{-5} (M)	3.9(E)
	Geraniol (106-24-1)	154.25	255.8 (M)	4(E)	1.15 x 10^{-5} (E)	3.5(E)

Substance(s)	Main components common name and CAS RN:	Molecular weight (g/mol) [a]	Water solubility (mg/L) [a]	VP (Pa) [a]	Henry's law constant (atm-m^3/mol) [a]	Log Kow [a]
Oils, Lemongrass	Total Citral (both isomers CAS RN 5392-40-5)	152.24	1340 at 37°C (E) *590 at 25°C (E)b*	12 (M) <130 at 40°C OECD TG 104 b	3.76 x 10^{-4} (M)	3.5 (M)
	Beta-myrcene (123-35-3)	136.24	5.6(E)	268(E)	6.43 x 10^{-2} (E)	4.17 (E)
	Geranyl acetate (105-87-3)	196.29	18.24(M)	4.4(E)	2.42 x 10^{-3} (M)	4(E)
	Citronellol (106-22-9)	156.27	105.5(M)	5.9(E)	5.68 x 10^{-5} (M)	3.9(E)
Oils, Sweet orange	Limonene (5989-27-5)	136.24	7.57 – 13.8 at 25°C(E)	192(E)	3.19 x 10^{-2} (E)	4.38-4.57(E)
Oils, Mandarin, Tangerine	Limonene (5989-27-5)	136.24	7.57 – 13.8 at 25°C(E)	192(E)	3.19 x 10^{-2} (E)	4.38-4.57(E)
	Total Citral (both isomers CAS RN 5392-40-5)	152	1340 at 37°C (E) *590 at 25°C (E)b*	12 (M) <130 at 40°C OECD TG 104 b	3.76 x 10^{-4} (M)	3.5(M)
	Linalool (78-70-6)	154.25	1590(E)	21(E)	2.15 x 10^{-5} (E)	2.9(E)
	Methyl N-methylanthranilate (85-91-6)	165.19	257 at 25°C(M)	2.78(M)	2.69 x 10^{-8} (M)	2.81 (M)
	Gamma-terpinene (99-85-4)	136.24	8.68 at 22°C(E)	145(E)	2.25 x 10^{-2} (E)	4.5(E)
	Alpha-terpinene (99-86-5)	136.24	5.92 at 25°C(M)	222(M)	3.65 x 10^{-1} (M)	4.25 (E)

Substance(s)	Main components common name and CAS RN:	Molecular weight (g/mol) [a]	Water solubility (mg/L) [a]	VP (Pa) [a]	Henry's law constant (atm-m^3/mol) [a]	Log Kow [a]
	Delta-terpinene (586-62-9)	136.24	9.5 at 23°C(E)	99(E)	1.40 x 10^{-2} (E)	4.47 (E)
Alpha-pinene	NA	136.24	2.49 at 25°C(E)	633(E)	1.07 x 10^{-1} (M)	4.44 – 4.83(E)
Turpentine oil & Turpentine	Alpha-pinene (80-56-8)	136.24	2.49 at 25°C(E)	633(E)	1.07 x 10^{-1} (M)	4.44 – 4.83 (E)
	Beta-pinene (127-91-3)	136.24	7.06 at 25°C(M)	391(E)	1.61 x 10^{-1} (M)	4.16(E)
	Limonene (5989-27-5)	136.24	7.57 – 13.8 at 25°C(E)	192(E)	3.19 x 10^{-2} (E)	4.38-4.57(E)
	Camphene (79-92-5)	136.24	4.6 at 25°C(E)	335(E)	1.61 x 10^{-1} (M)	4.22 (E)
Oils, Fir	Alpha-pinene (80-56-8)	136.24	2.49 at 25°C(E)	633(E)	1.07 x 10^{-1} (M)	4.44 – 4.83(E)
	Beta-pinene (127-91-3)	136.24	7.06 at 25°C(M)	391(E)	1.61 x 10^{-1} (M)	4.16(E)
	Limonene (5989-27-5)	136.24	7.57 – 13.8 at 25°C(E)	192(E)	3.19 x 10^{-2} (E)	4.38-4.57(E)
	Camphene (79-92-5)	136.24	4.6 at 25°C(E)	335(E)	1.61 x 10^{-1} (M)	4.22 (E)
Oils, Pine	Alpha-terpineol (98-55-5)	154.25	710 at 25°C(E)	5.64(E)	1.22 x 10^{-5} (E)	2.98-3.28(E)
	Alpha-pinene (80-56-8)	136.24	2.49 at 25°C(E)	633(E)	1.07 x 10^{-1} (M)	4.44 – 4.83(E)
	Beta-pinene (127-91-3)	136.24	7.06 at 25°C(M)	391(E)	1.61 x 10^{-1} (M)	4.16(E)
	Beta-myrcene (123-35-3)	136.24	5.6(E)	268(E)	6.43 x 10^{-2} (E)	4.17 (E)

Substance(s)	Main components common name and CAS RN:	Molecular weight (g/mol) [a]	Water solubility (mg/L) [a]	VP (Pa) [a]	Henry's law constant (atm-m^3/mol) [a]	Log Kow [a]
	Limonene (5989-27-5)	136.24	7.57 – 13.8 at 25°C[(E)]	192[(E)]	3.19 x 10^{-2} [(E)]	4.38-4.57[(E)]
	Camphene (79-92-5)	136.24	4.6 at 25°C[(E)]	335[(E)]	1.61 x 10^{-1} [(M)]	4.22 [(E)]

Abbreviations: Kow, octanol–water partition coefficient; NA, not available.
[(E)] Experimental
[(M)] Modelled
[a] US EPA 2012b
[b] From Citral OECD document

4. Environmental fate and behaviour

4.1 Environmental persistence

The majority of the substances in the Acyclic, Monocyclic and Bicyclic Monoterpenes Group are not expected to persist in air, water, soil or sediment (ECCC 2016b).

Bois de rose oil is expected to persist in water, soil and sediment but is not expected to persist in air (ECCC 2016b).

4.2 Potential for bioaccumulation

Although the log K_{ow} values for, bois de rose oil, palmarosa oil, coriander oil, rose oil, lemongrass oil, sweet orange oil, alpha-pinene, turpentine oil, turpentine and pine oil are slightly higher (log K_{ow} between 2 and 5), the bioconcentration factors for these substances are below 5 000 L/kg and as such they are not expected to significantly bioaccumulate in organisms (ECCC 2016b).

Given geranium oil, geranyllinalool, mandarin oil, tangerine oil, and fir oil had high bioconcentration factors (greater than 5 000 L/kg), (ECCC 2016b), these substances are expected to significantly bioaccumulate in organisms.

5. Potential to cause ecological harm

5.1 Characterization of ecological risk

The ecological risks of the substances in the Acyclic, Monocyclic and Bicyclic Monoterpenes 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 [LC_{50}]) 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 scientific literature, from available empirical databases (e.g., OECD QSAR Toolbox 2016), and from responses to surveys under section 71 of CEPA, or they were generated using selected (quantitative) structure-activity relationship ([Q]SAR) or mass-balance fate and bioaccumulation models. These data were used as inputs to other mass-balance models or to complete the substance hazard and exposure profiles.

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

A risk matrix was used to assign a low, moderate or high classification of potential risk for each substance 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 which had a low estimated rate of emission to water after wastewater treatment, representing a low potential for exposure. The second step reviewed low risk potential classification outcomes using relatively conservative, local-scale (i.e., in the area immediately surrounding a point-source of discharge) risk scenarios, designed to be protective of the environment, to determine whether the classification of potential risk should be increased.

ERC uses a weighted approach to minimize the potential for both over and under classification of hazard and exposure and subsequent risk. The balanced approaches for dealing with uncertainties are described in greater detail in ECCC 2016a. The following describes two of the more substantial areas of uncertainty. Error with empirical or modeled acute toxicity values could result in changes in classification of hazard, particularly metrics relying on tissue residue values (i.e., mode of toxic action), many of which are predicted values from (Q)SAR models (OECD QSAR Toolbox 2016). However, the impact of this error is mitigated by the fact that overestimation of median lethality will result in a conservative (protective) tissue residue used for critical body residue (CBR) analysis. Error with underestimation of acute toxicity will be mitigated

through the use of other hazard metrics such as structural profiling of mode of action, reactivity and/or estrogen binding affinity. Changes or errors in chemical quantity could result in differences in classification of exposure as the exposure and risk classifications are highly sensitive to emission rate and use quantity. The ERC classifications thus reflect exposure and risk in Canada on the basis of what is believed to be the current use quantity, and may not reflect future trends.

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

The hazard and exposure classifications for the substances in the Acyclic, Monocyclic and Bicyclic Monoterpenes Group are summarized in Table 5-1.

Table 5-1. Ecological risk classification results for the substances in the Acyclic, Monocyclic and Bicyclic Monoterpenes Group

Substance	ERC hazard classification	ERC exposure classification	ERC risk classification
Bois de rose oil	low	low	low
Palmarosa oil	low	low	low
Geranium oil	low	low	low
Geranyllinalool	low	low	low
Coriander oil	low	low	low
Rose oil	low	low	low
Lemongrass oil	low	low	low
Sweet orange oil	low	low	low
Mandarin oil	low	low	low
Tangerine oil	low	low	low
Alpha-pinene	moderate	low	low
Turpentine oil	low	low	low
Turpentine	low	low	low
Fir oil	low	low	low
Pine oil	moderate	low	low

On the basis of low hazard and low exposure classifications according to information considered under ERC, bois de rose oil, palmarosa oil, geranium oil, geranyllinalool, coriander oil, rose oil, lemongrass oil, sweet orange oil, mandarin oil, tangerine oil, turpentine oil, turpentine and fir oil were classified as having a low potential for ecological risk. It is unlikely that these substances are resulting in concerns for the environment in Canada.

According to information considered under ERC, alpha-pinene was classified as having a moderate hazard potential on the basis of having a moderate potential to cause adverse effects in aquatic food webs given its bioaccumulation potential. Pine oil was also classified as having a moderate hazard potential on the basis of an elevated

toxicity ratio. However, the potential effects and how they may manifest in the environment were not further investigated due to the low exposure of these substances. On the basis of current use patterns, these substances are unlikely to be resulting in concerns for the environment in Canada.

6. Human health assessment approach

Health effects characterization

For the health effects characterization of the acyclic and mono/bicyclic terpenes and terpenoids preference was given to hazard data on the whole oil itself. In the absence of quality hazard data on the whole oil, a main components approach was taken. Individual components that had hazard data available and that were present in significant concentrations (i.e., generally greater than 10%) were used to inform the health effects characterization.

Due to their limited hazard potential, bois de rose oil, palmarosa oil, geranium oil, geranyllinalool, sweet orange oil and/or their main components were evaluated using a qualitative approach.

A quantitative approach was taken for rose oil, coriander oil, lemongrass oil, mandarin/tangerine oil, alpha-pinene, turpentine/turpentine oil, fir and pine oil as critical health effects were identified for these substances.

Dermal absorption

Since the physical-chemical properties of the main components of the acyclic and mono/bicyclic terpenes and terpenoids are all similar, a group approach was taken whereby a single dermal absorption value is used to represent dermal absorption of all the acyclic and mono/bicyclic terpenes and terpenoids.

In vitro human dermal absorption studies for geraniol, citronellol, and linalool (Gilpin et al. 2010; ECHA 2018a) were identified. These studies indicated that dermal absorption would range from 4.3 to 19.5% (mean dermal absorption value + 1 or 2 standard deviations based on variability (SCCS 2010) depending on whether the site is occluded).

Two *in vivo* studies (Schuster et al. 1986; Jager et al. 1992) conducted in human subjects were identified. In these studies, serial plasma measurements were taken following dermal application of a cough medication containing alpha-pinene (n=12), and a massage oil containing linalool (n=1). Estimated dermal absorption values from these studies ranged from 31 to 42% and were higher than the *in vitro* studies; however, all of the terpenes and terpenoids have moderate to high vapour pressures and it is expected that a significant portion of the absorbed dose would be from the inhalation route. This is supported by the rapid absorption observed in the *in vivo* studies, where peak plasma

concentrations were obtained within 6 to 19 minutes, which is more consistent with a chemical being absorbed by the inhalation route. In addition, in one of the *in vitro* studies, a volatility assessment was performed and there was 93% evaporative loss over 1 hour and 97% over 24 hours (ECHA 2018a) suggesting that the majority of a dermally applied dose would be lost to evaporation and available for inhalation.

Based on the available information, an upper bound estimate of dermal absorption from the *in vitro* studies of 20% and 4% for occluded and unoccluded skin sites, were identified. The selected values are representative of the amount absorbed by the dermal route over the twenty-four hour exposure duration and also take into account that a portion of the applied dose volatilized during the study. As the *in vivo* human studies suggest that inhalation may also be a route of exposure, an inhalation risk assessment is also conducted assuming that the remainder of the applied dose (80% or 96% for occluded, unoccluded sites, respectively) is available for evaporation, and potentially absorbed by the inhalation route.

For body lotion and non-medicinal ingredient in topical medicated vapour product scenarios, a dermal absorption value of 20% for occluded skin conditions was used, as there was no dermal absorption value available that represented semi-occluded skin conditions. The massage oil scenario was considered representative of an unoccluded scenario during the massage itself, and a semi-occluded scenario following the massage when the individual would be clothed. Since the results from the in vitro dermal absorption study suggests that there is significant evaporative loss during the first hour following dermal application (93%, ECHA 2018a), it was determined that use of unoccluded skin conditions to represent the massage oil scenario (i.e. 4% dermal absorption) was appropriate. For all other scenarios (e.g., face moisturizer, sunscreen, and cleaning scenarios), the skin was considered to be unoccluded and the dermal absorption value of 4% for unoccluded skin conditions was used.

Route-to-route extrapolation

In the absence of route-specific health effects data, a route-to-route extrapolation approach was used in quantitative risk characterization. When extrapolating from the inhalation or oral route, bioavailablity by the inhalation and oral routes were assumed to be equivalent. When a use scenario resulted in exposure by more than one route of exposure (e.g. dermal, inhalation, or oral) and the critical health effect was applicable to all routes, exposure was calculated by summing systemic exposures by all relevant routes of exposure.

7. Acyclic monoterpenes

7.1 Bois de rose oil

7.1.1 Sources and uses

Bois de rose oil is a naturally occurring substance that is derived from steam distillation of the wood from *Aniba rosaeodora*, native mainly to Brazil, Peru and French Guinea (Burdock 2010).

Based on information submitted pursuant to a section 71 survey under CEPA (Canada 2012), there were no reports of import or manufacture above the reporting threshold of 100 kg for bois de rose oil in 2011 (Environment Canada 2013).

Bois de rose oil is used in a number of cosmetic products such as skin and hair care products (lotions/cleansers), fragrances, deodorants and massage products. It is also used in aromatherapy, and is listed as a fragrance ingredient used in consumer goods by the International Fragrance Association (IFRA 2017).

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, Bois de rose oil, *Aniba rosaeodora* oil, *Aniba rosodora* oil, or rosewood oil are used in a wide range of cosmetic products in Canada (personal communication, emails from the Consumer Product Safety Directorate, 2017; unreferenced). In addition, rosewood essential oil and *Aniba rosaeodora* (rosewood) wood oil are present as medicinal and non-medicinal ingredients in many natural health products, respectively (email from Natural and Non-Prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, July 2015; unreferenced).

Bois de rose oil has reported uses in food including alcoholic and non-alcoholic beverages, baked goods, frozen dairy, gelatins/puddings, meat products and candy/chewing gum (Burdock 2010). Bois de rose oil is listed in the US FDA Substances Added to Food inventory and in the Food Chemicals Codex as a flavouring agent (US FDA 2018; FCC 2018). No definitive information is available concerning the potential use of bois de rose oil as a food flavouring agent in Canada however since the substance is known to be used as a food flavouring agent in the US, it is possible that the substance is present as a flavouring agent in foods sold in Canada.

Additional uses for bois de rose oil are listed in Table 7.1-1.

Table 7.1-1. Additional uses in Canada for bois de rose oil

Use	Details
Food flavouring[a]	Reported uses in alcoholic and non-alcoholic beverages, baked goods, frozen dairy, gelatins/puddings, meat products and candy/chewing gum (Burdock 2010)
Natural Health Products Ingredients Database[b]	MI, NMI (cosmetic astringent, fragrance ingredient or skin-conditioning agent in topical products, flavour enhancer in oral products)
Licensed Natural Health Products Database being present as a medicinal or non-medicinal ingredient in natural health products in Canada[b]	MI, NMI
Notified to be present in cosmetics, based on notifications submitted under the *Cosmetic Regulations* to Health Canada[c]	Skin and hair care products, fragrances, and deodorants.
Formulant in pest control products registered in Canada[d]	Formulant

Abbreviations: MI, medicinal ingredient; NMI, non-medicinal ingredient.

[a] Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced; Burdock 2010

[b] Email communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[c] Email communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[d] Email communication from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau; unreferenced

7.1.2 **Potential to cause harm to human health**

In consideration of the low quantities (<100 kg) of the substance reported to be used in Canada (Environment Canada 2013), an impact on human health from exposure to bois de rose oil from environmental media is not expected.

No relevant health effects studies have been identified for bois de rose oil. Consequently, the health effects information for linalool, the main component of bois de rose oil which comprises 81-99% of the oil, is used to inform the risk assessment.

Linalool has been reviewed internationally in an OECD SIDS Initial Assessment Report (OECD/SIDS 2002). In terms of subchronic and reproductive toxicity in mammals, linalool was concluded to be of “moderate to low” toxicity. This determination was based primarily on two studies conducted with coriander oil (containing 72.9% linalool). In the first study, effects of low severity (no adverse) (e.g., changes in serum proteins and liver and kidney histology) were observed following the exposure of rats to 160, 400, or 1 000 mg/kg bw/day coriander oil for 28 days via gavage. A NOAEL of 160 mg/kg bw/day was established for these effects (OECD/SIDS 2002, Burdock et al. 2009, Letizia et al.

2003). In the second study, female rats were administered via gavage to 250, 500, or 1000 mg/kg bw/day seven days prior to co-habitation through to four days post parturition. No effect on reproductive parameters was observed. Adverse effects on fetal development were considered to occur only in the presence of maternal toxicity at 1 000 mg/kg bw/day based on decreased litter size and increased pup morbidity/mortality. Therefore, a NOAEL of 250 mg/kg bw/day has been defined (Letizia et al. 2003). Effects on offspring were only observed at levels that also caused maternal toxicity and consequently, linalool was not considered to present a reproductive or developmental hazard (Letizia et al. 2003).

Although the OECD reviewed linalool in the OECD SIDS initial assessment report, their assessments on the repeated dose and developmental toxicity end points focused largely on studies conducted with coriander oil rather than pure linalool. Given the uncertainty in extrapolating from coriander oil to linalool/bois de rose oil, and the recent availability of quality data for linalool itself published after the OECD SIDS, the point of departures identified in the OECD studies were not considered relevant for the present assessment.

Another study considered by the OECD evaluated the effect of linalool on drug metabolizing enzymes following the administration of rats to a single dose of 500 mg/kg bw/day for 64 days (OECD/SIDS 2002). In terms of genotoxicity or carcinogenicity, no concerns were identified for linalool in the report. In addition, despite short term loads on the liver due to enterohepatic circulation, linalool is expected to be rapidly excreted in the urine. As a result of all of these considerations, the OECD deemed the overall toxicity of linalool to be low.

A literature search for linalool data more recent than that considered in the OECD/SIDS 2002 SIDS Assessment was carried out. In a developmental toxicity study, rats were administered 0, 250, 500 or 1 000 mg/kg bw/day linalool via gavage on gestational days 7 to 17. The animals showed no adverse effects up to 1000 mg/kg bw/day linalool, aside from a non-significant decrease in maternal body weight and significant reduction in feed consumption during GD 7-10 which were reversed upon cessation of chemical treatment (GD 18-21). The authors determined a maternal NOAEL of 500 mg/kg bw/day for these effects and it was concluded that, at the doses tested, linalool was not a developmental toxicant in rats (Politano et al. 2008). Although this study did not find any concerns for developmental toxicity, the authors noted a maternal NOAEL of 500 mg/kg bw/day for a non-significant decrease in maternal body weight and a significant reduction in feed consumption during GD 7-10 at the 1 000 mg/kg bw/day dose level. Given the lack of developmental effects up to 1 000 mg/kg bw/day and the fact that maternal effects were reversed upon cessation of chemical treatment, the outcomes observed in this study are not considered to be adverse.

An unpublished study report submitted to the Research Institute for Fragrance Materials (RIFM) was also identified from the literature. The details of the study were not available for independent evaluation; however, summaries were available in published peer reviewed journals. In this study, rats were dermally administered 250, 1 000, and 4 000

mg/kg bw/day linalool for 90 days. A NOAEL of 250 mg/kg bw/day was established by the authors based on depressed body weights (no specific data available) in female rats only at the 1 000 mg/kg bw/day dose level (Letizia et al. 2003). Health Canada's Pest Management Regulatory Agency (PMRA) had conservatively set the LOAEL of this study at 250 mg/kg bw/day based on slight erythema (that cleared after three weeks) and slight and sporadic depressed activity in the rats. However, given the reversibility of the dermal effects and the non-significant depressed activity, the current assessment considered the dose of 250 mg/kg bw/day as the NOAEL.

Evaluations of both linalool and Bois de Rose Oil by the Joint FAO/WHO Expert Committee on Food Additives have concluded that they do not present a safety concern as a food flavouring agents based on estimated levels of intake (WHO 2004a). Bois de rose oil has also been classified by the US Food and Drug Administration (FDA) as being generally recognized as safe (GRAS) when used as flavouring agent or adjuvant (US FDA 2017a).

Based on available information, health effects of concern were not identified. Accordingly, points of departure were not defined and a qualitative approach to risk characterization was taken. Exposure of the general population to bois de rose oil is, therefore, considered to be of low risk to human health.

7.2 Palmarosa oil

7.2.1 Sources and uses

Palmarosa oil is a naturally occurring substance that is derived from the *Cymbopogon martini* plant (Rajeswara et al. 2009).

Based on information submitted pursuant to a section 71 survey under CEPA (Canada 2012), there were no reports of import or manufacture above the reporting threshold of 100 kg for palmarosa oil in 2011 (Environment Canada 2013). It was, however, reported as being imported into or manufactured in Canada in quantities below or equal to the reporting threshold.

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, Palmarosa oil or *Cymbopogon martini oil* is used in a wide range of cosmetic products in Canada, such as skin and hair care products (lotions/cleansers), fragrances, deodorants and massage products (personal communication, emails from the Consumer Product Safety Directorate, 2017; unreferenced); palmarosa essential oil is also present as a medicinal and non-medicinal ingredient in many natural health products (email from Natural and Non-Prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, July 2015; unreferenced).

Palmarosa oil is also listed as a fragrance ingredient used in consumer goods by the International Fragrance Association (IFRA 2017).

Information from the American Cleaning Institute's (ACI) website indicates potential use of palmarosa oil in household cleaning products including all-purpose cleaners and dish and laundry care products (ACI 2017).

Palmarosa oil has reported uses as a flavouring agent in foods including alcoholic and non-alcoholic beverages, baked goods, frozen dairy, gelatins/puddings and candy (Burdock 2010). Palmarosa oil is listed in the US FDA Substances Added to Food inventory and in the Food Chemicals Codex as a flavouring agent (US FDA 2018; FCC 2018). No definitive information is available concerning the potential use of palmarosa oil as a food flavouring agent in Canada; however since the substance is known to be used as a food flavouring agent in the US, it is possible that the substance is present as a flavouring agent in foods sold in Canada.

Additional uses for palmarosa oil are listed in Table 7.2-1.

Table 7.2-1. Additional uses in Canada for palmarosa oil

Use	Details
Food flavouring[a]	Reported uses in alcoholic and non-alcoholic beverages, baked goods, frozen dairy, gelatins/puddings and candy (Burdock 2010).
Natural Health Products Ingredients Database[b]	MI, NMI (fragrance ingredient, flavour enhancer)
Licensed Natural Health Products Database being present as a medicinal or non-medicinal ingredient in natural health products in Canada[b]	MI, NMI
Notified to be present in cosmetics, based on notifications submitted under the *Cosmetic Regulations* to Health Canada[c]	Skin and hair care products, fragrances, deodorants, and massage products.
Formulant in pest control products registered in Canada[d]	Formulant

Abbreviations: MI, medicinal ingredient; NMI, non-medicinal ingredient.
[a] Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced; Burdock 2010
[b] Email communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced
[c] Email communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau; unreferenced
[d] Email communication from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau; unreferenced

7.2.2 **Potential to cause harm to human health**

In consideration of the low quantities (<100 kg) of the substance reported to be used in Canada (Environment Canada 2013), an impact on human health from exposure to palmarosa oil from environmental media is not expected.

Limited health effects information is available for palmarosa oil. In an inhalation study, male rats were administered a single dose of 13.73 mg/L palmarosa oil for 10 minutes every 48 hours for 30 days. Adverse effects were not identified in this study (Andrade et al. 2014). To inform risk characterization, the health effects information available for the main components of palmarosa oil, geraniol (70-92%) and geranyl acetate (4-16%), have been considered.

In terms of geraniol, a human health effects assessment was conducted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) in Australia (NICNAS 2012). This review found no concerns for genotoxicity following several in vitro assays, and based on these findings, geraniol was considered by NICNAS not likely to be carcinogenic. Geraniol was not considered to be a reproductive or developmental toxicant based on a combined repeated dose and reproductive developmental toxicity screening test conducted in rats dermally administered 0, 50, 150 or 450 mg/kg bw/day. Effects observed in this study were limited to local inflammatory reactions. Further oral repeated dose studies in rats confirmed no adverse effects up to 550 mg/kg bw/day. NICNAS (2012) concluded that the main critical health effects of geraniol were local eye and skin irritation and skin sensitization.

Geranyl acetate underwent a screening-level hazard characterization by the US EPA in 2009 as a sponsored chemical (part of the Terpenoid Primary Alcohols and Related Esters Category) under the High Production Volume (HPV) Challenge Program (US EPA 2009). Toxicity studies for geranyl acetate did not show concerns for genotoxicity. Adverse effects were not reported up to the highest dose tested of approximately 500 mg/kg bw/day in a 17-week repeated dose study in rats involving a mixture of geranyl acetate and citronellyl acetate in the diet (Hagan et al. 1967). Adverse effects were reported at 2000 mg/kg bw/day and above (equivalent to 1 400 mg/kg bw/day geranyl acetate) in a 13-week oral repeated dose study of food grade geranyl acetate (i.e., containing 71% geranyl acetate and 29% citronellyl acetate) in male and female rats and mice. The effects included decreased body weights, stomach lesions, vacuolization of the liver, kidney and myocardium as well as increased incidences of death (NTP 1987). Carcinogenicity was not reported in a two-year gavage study in male and female rats and mice (1 000 or 2 000 mg/kg-day in rats and 500 or 1 000 mg/kg bw/day in mice). However, this study was limited by reduced animal survival in some groups (NTP 1987).

Geraniol and geranyl acetate have been evaluated internationally by the Joint FAO/WHO Expert Committee on Food Additives and are not considered to present a safety concern as food flavourings based on estimated intake levels (WHO 2004a). Palmarosa oil itself has been classified by the US FDA as being generally recognized as safe (GRAS) when used as flavouring agent or adjuvant (US FDA 2017a).

Based on available information, health effects of concern were not identified. Accordingly, points of departure were not defined and a qualitative approach to risk characterization was taken. Exposure of the general population to palmarosa oil is, therefore, considered to be of low risk to human health.

7.3 Geranium oil

7.3.1 Sources and uses

Geranium oil is a naturally occurring substance that is derived from steam distillation of the stems, leaves and flowers of various *Pelargonium spp.*, mainly produced in Africa and China (Gupta 2001; CBI 2014).

Based on information submitted pursuant to a section 71 survey under CEPA (Canada 2012), there were no reports of import or manufacture above the reporting threshold of 100 kg for geranium oil in 2011 (Environment Canada 2013). It was, however, reported as being imported into or manufactured in Canada in quantities below or equal to the reporting threshold.

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, geranium oil, rose geranium extract, rose geranium flower oil, rose geranium oil, geranium maculatum oil, *Pelargonium graveolens* oil/flower/extract/leaf/steam extract is used in a wide range of cosmetic products in Canada, such as, skin and hair care products (sunscreens/lotions/cleansers), fragrances, deodorants and massage products (personal communication, emails from the Consumer Product Safety Directorate, 2015; unreferenced); geranium essential oil is also present as medicinal and non-medicinal ingredients in many natural health products and drugs (emails from Natural and Non-Prescription Health Products Directorate and Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, March 2017 and June 2015, respectively; unreferenced).

Geranium oil is also listed as a fragrance ingredient used in consumer goods by the International Fragrance Association (IFRA 2017).

Geranium oil is listed in the US FDA Substances Added to Food inventory and in the Food Chemicals Codex as a flavouring agent (US FDA 2018; FCC 2018). No definitive information is available concerning the potential use of geranium oil as a food flavouring agent in Canada; however since the substance is known to be used as a food flavouring agent in the US, it is possible that the substance is present as a flavouring agent in foods sold in Canada.

Additional uses for geranium oil are listed in Table 7.3-1.

Table 7.3-1. Additional uses in Canada for geranium oil

Use	Details
Food flavouring[a]	Listed in the US FDA Substances Added to Food inventory and in the Food Chemicals Codex (US FDA 2018; FCC 2018)

Use	Details
Drug Products Database[b]	NMI (skin creams, oral anti-fungal product)
Natural Health Products Ingredients Database[c]	MI, NMI (fragrance in topical products, flavor enhancer in oral products)
Licensed Natural Health Products Database being present as a medicinal or non-medicinal ingredient in natural health products in Canada[c]	MI, NMI
Notified to be present in cosmetics, based on notifications submitted under the *Cosmetic Regulations* to Health Canada[d]	Skin and hair care products, fragrances, and deodorants.
Formulant in pest control products registered in Canada[e]	Active ingredient and formulant

Abbreviations: MI, medicinal ingredient; NMI, non-medicinal ingredient.

[a] Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced; US FDA 2018; FCC 2018.

[b] Email communication from Therapeutic Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[c] Email communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[d] Email communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[e] Email communication from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau; unreferenced

7.3.2 **Potential to cause harm to human health**

In consideration of the low quantities (<100 kg) of the substance reported to be used in Canada (Environment Canada 2013), an impact on human health from exposure to geranium oil from environmental media is not expected.

Studies on genotoxicity, carcinogenicity or reproductive/developmental effects were not identified. Consequently, in order to inform the risk assessment, the hazard information available for the main components of geranium oil, citronellol (37-48%), geraniol (20-30%) and linalool (5-14%) have been considered.

Genotoxicity or developmental effects were not identified in an in vivo mammalian erythrocyte micronucleus test and in a developmental toxicity study in rats following oral administration of up to 750 mg/kg bw/day citronellol (ECHA 2016). In another study, groups of 10 male and 10 female rats were given diets containing equal parts (by weight) of citronellol and linalool at concentrations intended to provide a dose of 0, or 100 mg/kg bw per day (50 mg of each substance) for 12 weeks. The actual average intake was 102 mg/kg bw/day (51 mg of each substance) for males and 112 mg/kg bw per day (56 mg of each substance) for females. Based on the absence of adverse effects at the highest dose of citronellol tested, the NOEL was determined to be 51

mg/kg bw/day in male rats and 56 mg/kg bw/day in female rats by the author (WHO 2004a).

In terms of geraniol, this substance was assessed by Australia (NICNAS 2012) and only health effects reported were eye and skin irritation and skin sensitization. Further information on the health effects of geraniol are provided in the Potential to cause harm to human health section of this document for palmarosa oil (Section 7.2.2).

A third component of geranium oil, linalool, was reviewed internationally in an OECD SIDS Initial Assessment Report (OECD/SIDS 2002) which deemed the overall toxicity of linalool to be low. Other studies published subsequent to OECD/SIDS 2002 did not identify concerns for developmental toxicity or for effects following dermal repeated dosing up to 1000 mg/kg bw/day. Further information on the health effects of linalool are provided in the Potential to cause harm to human health section for bois de rose oil (Section 7.1.2).

Citronellol, geraniol and linalool have been evaluated internationally by the Joint FAO/WHO Expert Committee on Food Additives and are not considered to present a safety concern as food flavourings based on estimated levels of intake (WHO 2004a). Geranium oil itself has also been classified by the US Food and Drug Administration (FDA) as being generally recognized as safe (GRAS) when used as flavouring agent or adjuvant (US FDA 2017a).

Based on available information, health effects of concern were not identified. Accordingly, points of departure were not defined and a qualitative approach to risk characterization was taken. Exposure of the general population to geranium is, therefore, considered to be of low risk to human health.

7.4 Geranyllinalool

7.4.1 Sources and uses

Geranyllinalool is a naturally occurring substance found as a component in a number of essential oils including champaca concrete, jasmine absolute and witch hazel leaf oil (Goodscents 2017).

Based on information submitted pursuant to a section 71 survey under CEPA (Canada 2012), there were no reports of import or manufacture above the reporting threshold of 100 kg for geranyllinalool in 2011 (Environment Canada 2013). It was, however, reported as being imported into or manufactured in Canada in quantities below or equal to the reporting threshold.

Information obtained pursuant to a section 71 survey under CEPA reported uses of geranyllinalool in personal care products (Environment Canada 2013). It is primarily

used as a fragrance ingredient in personal care products[7] (cosmetics, fragrances, shampoos, soaps) and household cleaners and detergents (Lapczynski et al. 2008). In Canada, geranyllinalool was not reported in cosmetic products based on notifications submitted under the *Cosmetic Regulations* to Health Canada. In Europe, geranyllinalool is reported as being used in cosmetics with a perfuming function (COSING 2017). It is also listed as a fragrance ingredient used in consumer goods by the International Fragrance Association (IFRA 2017).

In Europe, geranyllinalool is a flavouring substance approved for use in food (EU Food Flavourings Database 2016). No definitive information is available concerning the potential use of geranyllinalool as a food flavouring agent in Canada; however since the substance is permitted to be used a food flavouring agent in the EU, it is possible that the substance is present as a flavouring agent in foods sold in Canada.

Additional uses for geranyllinalool are listed in Table 7.4-1.

Table 7.4-1. Additional uses in Canada for geranyllinalool

Use	Details
Food flavouring[a]	Approved for use in Europe (EU Flavouring Database 2016)

[a] Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced; EU Flavouring Databse 2016

7.4.2 **Potential to cause harm to human health**

In consideration of the low quantities (<100 kg) of the substance reported to be used in Canada (Environment Canada 2013), an impact on human health from exposure to geranyllinalool from environmental media is not expected.

The European Food Safety Authority (EFSA) has determined that geranyllinalool does not pose a safety concern when used as flavouring substances at estimated levels of intake (EFSA 2015b). No relevant toxicity studies (e.g. subchronic, reproductive and developmental) have been identified on the literature for geranyllinalool.

Twenty-nine volunteers were dermally administered 1% (690 µg/cm^2) geranyllinalool in petrolatum to a normal site on their backs for 48h or 72h under occlusion. No irritation or sensitization was observed (RIFM 1982b; Lapczynski et al. 2008). No inhalation studies were identified.

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

In the absence of genotoxicity, carcinogenicity or reproductive/developmental toxicity of geranyllinalool, European Food Safety Authority (EFSA) has used linalool (which has an isolated terminal double bond in close proximity to the tertiary alcohol group) as a supporting substance to inform the toxicity of geranyllinalool (EFSA 2012). Linalool was reviewed internationally in an OECD SIDS Initial Assessment Report (OECD/SIDS 2002) and its overall toxicity was deemed to be low. Other studies not reviewed in the report also found no concerns for developmental toxicity or for dermal repeated dosing up to 1 000 mg/kg bw/day. Further information on the health effects of linalool are provided in the Potential to cause harm to human health section of this document for bois de rose oil (Section 7.1.2).

Based on available information, health effects of concern were not identified. Accordingly, points of departure were not defined and a qualitative approach to risk characterization was taken. Exposure of the general population to geranyllinalool is, therefore, considered to be of low risk to human health.

7.5 Coriander oil

7.5.1 Sources and uses

Coriander oil is a naturally occurring substance that is derived from steam distillation of various parts of the *Coriandrum sativum* L. plant (Mandal and Mandal 2015). The composition of the essential oil obtained from the different parts of the plant (i.e., seeds, fruits or leaves) can vary considerably (Mandal and Mandal 2015).

Based on information submitted pursuant to a section 71 survey under CEPA (Canada 2012), there were no reports of manufacture above the reporting threshold of 100 kg for coriander oil in 2011 (Environment Canada 2013). Between 100 and 1 000 kg of coriander oil was imported into Canada during the same calendar year.

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, coriander oil, *Coriandrum Sativum* (Coriander) fruit oil, is used in greater than 150 cosmetic products in Canada at concentrations ranging from <0.1%-100% (personal communication, emails from the Consumer Product Safety Directorate, 2017; unreferenced). Some of the product types reported include body lotion, massage products, cleansers, fragrance, make-up, hair care, and bath products. The majority of products (>75%) contain coriander oil at a concentration of 1% or less. In general, products with higher concentrations of coriander oil are intended to be diluted prior to use (personal communication, emails from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

In Canada, coriander oil is used in cosmetic products such as skin and hair care products (sunscreens/lotions/cleansers), fragrances, deodorants and massage

products. Information obtained pursuant to a section 71 survey under CEPA also reported uses in imported personal care products as well as drugs (Environment Canada 2013). In addition, cilantro leaf oil, coriander seed essential oil, and coriandrum sativum (coriander) fruit oil may be present in natural health products as either medicinal or non-medicinal ingredients (personal communication from Natural and Non-Prescription Health Products Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). It is also listed as a fragrance ingredient used in consumer goods by the International Fragrance Association (IFRA 2017).

Known also as cilantro, the leaves and seeds of the coriander plant are used for adding flavour to food (Laribi et al. 2015). In the US, coriander oil is used in alcoholic and non-alcoholic beverages, condiments, meat products, baked goods, candy/chewing gum, dairy, gelatins/puddings and confection/frosting (Burdock 2010). Coriander oil is listed in the US FDA Substances Added to Food inventory and in the Food Chemicals Codex as a flavouring agent (US FDA 2018; FCC 2018). No definitive information is available concerning the potential use of coriander oil as a food flavouring agent in Canada however since the substance is known to be used as a food flavouring agent in the US, it is possible that the substance is present as a flavouring agent in foods sold in Canada.

Additional uses for coriander oil are listed in Table 7.5-1.

Table 7.5-1. Additional uses in Canada for coriander oil

Use	Details
Food flavouring[a]	Reported uses in alcoholic and non-alcoholic beverages, condiments, meat products, baked goods, candy/chewing gum, dairy, gelatins/puddings and confection/frosting (Burdock 2010).
Incidental additives[a]	Component in an anti-insecticide to be used in food processing establishments. No potential for food contact.
Drug Products Database[b]	NMI (sunscreen, ethanolamine derivatives)
Natural Health Products Ingredients Database[c]	NMI (flavor enhancer, fragrance ingredient)
Licensed Natural Health Products Database being present as a medicinal or non-medicinal ingredient in natural health products in Canada[c]	NMI
Notified to be present in cosmetics, based on notifications submitted	

Use	Details
under the *Cosmetic Regulations* to Health Canada[d]	Skin and hair care products, fragrances, and deodorants.
Formulant in pest control products registered in Canada[e]	Formulant

Abbreviations: NMI, non-medicinal ingredient.
[a] Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced; Burdock 2010
[b] Email communication from Therapeutic Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced
[c] Email communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced
[d] Email communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau; unreferenced
[e] Email communication from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau; unreferenced

7.5.2 **Potential to cause harm to human health**

7.5.2.1 Exposure assessment

In consideration of the low quantities of the substance reported to be used in Canada (Environment Canada 2013), an impact on human health from exposure to coriander oil from environmental media is not expected.

Dietary exposure of Canadians to coriander oil when used as a food flavouring agent was estimated using the individual consumption of 4.92×10^{-2} mg/kg bw/day for the US population established in Fenaroli's Handbook of Flavor Ingredients (personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2017; unreferenced).

To evaluate the potential for exposure to coriander oil from cosmetics applied by the dermal route, sentinel scenarios were selected based on a combination of use frequencies and reported concentrations of coriander oil in these products. These scenarios represented the highest exposure, relative to other dermally applied cosmetics and natural health products based on identified products reported to contain the substance. Exposure to coriander oil from the use of a body moisturizer and massage oil were considered to be the sentinel scenarios for dermal applications. These data are summarized in Appendix A (Tables A-1 and A-2).

The highest daily exposure to coriander oil is expected to occur from the use of a body moisturizer with reported upper concentration of 3% coriander oil. Systemic exposure by the dermal and inhalation route for body moisturizer (assuming 20% dermal absorption) ranged from 7.20×10^{-1} to 1.60 mg/kg bw/day (adults to infants) (emails from the Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau, 2016 and 2018; unreferenced). Systemic exposure by the dermal and inhalation route for massage oil (calculated from 2 drops of oil [label directions] from 30% upper concentration) ranged from 1.72×10^{-2} – 1.42×10^{-1} mg/kg bw/day (adult to infant) (dermal and inhalation). In addition, there are a few TPD and NNHPD products where coriander oil is present as a non-medicinal ingredient. These products include face

moisturizers or concealers containing a sunscreen agent, foundations, shampoo and muscle pain relievers; however, exposure to coriander oil from these products is assumed to be less than the highest estimates of dermal exposure from use of a 3% body moisturizer based on product amount per use and use frequencies (email from Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, Jan 2017; unreferenced).

One therapeutic product administered by the oral route contains 0.2 mg coriander oil as a non-medicinal ingredient in a cold medication (email from Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, April 2018; unreferenced). The highest systemic exposure from this product was calculated to be 5.00×10^{-2} mg/kg bw/day for children equal to or older than 12 years of age assuming 0.2 mg of coriander oil is present in each 5 mL dose taken (with a maximum of 80mL allowed per day) and the average body weight of a teen being 59.4 kg (HC 1998). Systemic exposure for children 6 to 12 years of age to adults ranged from 5.16×10^{-2} to 4.51×10^{-2} mg/kg bw/day, respectively.

Exposure to coriander oil by the inhalation route is expected from the use of certain cosmetics (e.g., spray perfume) and aromatherapy. Mean concentration on day of exposure from a perfume containing 10% coriander oil was determined to be 0.019 mg/m^3 (or systemic exposure ranging from 4.30×10^{-3} – 8.90×10^{-3} mg/kg bw/day) (adults to 5-year-olds) (full calculation parameters in Appendix-A, Table A-3). Inhalation exposure to coriander oil from an aromatherapy diffuser was calculated using a Danish EPA health assessment document of chemical substances in essential oils and fragrance oils (Danish EPA 2008). Details of the scenario and exposure parameters are outlined in Appendix D (Tables D1-D2). Systemic exposure ranges from 6.00×10^{-2} – 1.50×10^{-1} mg/kg bw/day were calculated for coriander oil.

7.5.2.2 Health effects assessment

Hazard assessment of coriander oil

Coriander oil has been classified by the US FDA as being generally recognized as safe (GRAS) when used as food flavouring agent or adjuvant (US FDA 2017a). Such classifications are based on chemical identity of a substance (congeneric groupings) and knowledge about the metabolic fate.

Limited information is available regarding the health effects of coriander oil. Two unpublished study reports submitted to the Research Institute for Fragrance Materials (RIFM) in 1990 were identified in peer reviewed journals and an OECD SIDS (Belsito et al. 2008, OECD/SIDS 2002).

In a repeated dose study, male and female rats were administered orally via gavage to 160, 400, 1 000 mg/kg bw/day coriander oil in 1% methylcellulose for 28 days (Belsito et al. 2008, Burdock and Carabin 2009, Letizia et al. 2003, OECD/SIDS 2002). No changes were seen in survival, clinical observations, body weights or food consumption

at any dose. However, an increase in serum proteins and serum albumin in blood, liver and kidney weights along with histopathological observations such as degenerative lesions in the renal cortex and periportal hepatocellular cytoplasmic vacuolization in the liver were reported at 400 or 1 000 mg/kg bw/day. A NOAEL of 160 mg/kg bw/day was established by the authors based on the increase of liver and kidney weights and the histopathological observations.

In a reproductive and developmental study, female rats were administered orally to 250, 500, or 1 000 mg/kg bw/day coriander oil seven days prior to co-habitation through four days post parturition (Letizia et al. 2003). The authors reported an increase in salivation, urine stained fur, decreased motor function and increase in body weight in dams at 500 and 1000 mg/kg bw/day. A NOAEL of 250 mg/kg bw/day was reported based on maternal effects. The developmental effects included a decrease in litter size and an increase in pup morbidity/mortality at the highest dose. Coriander oil does not seem to affect the reproductive performance of the female or the development of the offspring in the absence of significant effects of the toxicity in the dams. The effects in offspring were only observed at a dose which caused maternal toxicity; therefore, coriander oil was not considered a reproductive or developmental hazard by the authors.

A genotoxicity study was negative (Burdock and Carabin 2009).

In order to further inform the risk assessment, the health effects information available for the main components of coriander oil from seeds, linalool (59-88%), geranyl acetate (0-46%),and alpha-pinene (0.1-11%) have been considered.

Hazard assessment of main components

Geranyl acetate and linalool have been evaluated internationally by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and are not considered to present a safety concern as food flavourings based on estimated intake levels (WHO 2004a).

A review of the literature of linalool and geranyl acetate found no concerns for genotoxicity or carcinogenicity. Moreover, no adverse effects were reported below 1 000 mg/kg bw/day in reproductive/developmental or repeated dose studies. Further information on linalool and geranyl acetate is provided in the Potential to cause harm to human health section for bois de rose oil and palmarosa oil (Section 7.1.2 and 7.2.2), respectively.

Alpha-pinene was reviewed by the US EPA in 2010 as a sponsored chemical (part of the Bicyclic Terpene Hydrocarbons category) under the HPV Challenge Program (US EPA 2009), which established a NOAEC of 50 ppm and LOAEC of 100 ppm. Further information on the health effects of alpha-pinene is in the Health effects assessment section for alpha-pinene (Section 8.3.2).

7.5.2.3 Characterization of risk to human health

A NOAEL of 160 mg/kg bw/day has been identified based on effects in the kidney and liver and changes in serum biochemistry following oral exposure to 400 mg/kg bw/day of coriander oil in a 28-day study in rat (OECD/SIDS 2002). No hazard data was identified for the dermal and inhalation routes of exposure to coriander oil. Therefore, the oral NOAEL of 160 mg/kg bw/day was used for characterization of risk along with route-to-route extrapolation. It was assumed that absorption of coriander oil via inhalation was equivalent to absorption via the oral route.

Table 7.5-2. Relevant exposure estimates, critical effect levels and resulting margins of exposure, for coriander oil

Exposure Scenario[a]	**Systemic Exposure (mg/kg bw/day)**	**MOE[b]**
Food flavouring (dietary intake)	4.90×10^{-2} (6 months and above)	3 265 (6 months and above)
Systemic exposure by the dermal and inhalation routes from body lotion (3%)[c]	7.16×10^{-1} – 1.60 (adult-infant)	100 - 224 (infant-adult)
Systemic exposure by the dermal and inhalation routes massage oil scenario (2 drops from 30% upper concentration)[d]	1.72×10^{-2} – 1.42×10^{-1} (adult-infant)	1 125 - 9 300 (infant-adult)
Systemic exposure by the inhalation route from fragrance product (10%)	4.30×10^{-3} – 8.90×10^{-3} (adult-5 to 11 yrs)	17 977 - 37 209 (5 to 11 yrs– adult)
Oral exposure from cold medication (0.2mg)	4.50×10^{-2} – 5.40×10^{-2} (6 yrs and above)	2 963 - 3 555 (6 yrs and above)
Systemic exposure by the inhalation route from aromatherapy [e]	6.00×10^{-2} – 1.50×10^{-1} (all age groups)	1 066 - 2 666 (all age groups)

[a] Exposure scenario parameters and calculations for coriander oil outlined in Appendix A
[b] Margin of exposure calculated using a critical effect level (NOAEL = 160 mg/kg bw/day) for coriander oil based on hepatocellular cytoplasmic vacuolization, degenerative lesions in the renal cortex, and changes in serum biochemistry from a 28 day oral study in rats.
[c] Assuming dermal absorption of 20% (occluded)
[d] Assuming dermal absorption of 4% (unoccluded)
[e] Refer to Appendix D for Aromatherapy Scenario details

For all scenarios, the margins of exposure (MOE) between the critical effect level and the estimate of exposure are considered adequate to account for uncertainties in the health effects and exposure databases.

7.5.2.4 Uncertainties in evaluation of risk to human health

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

Table 7.5-3. Sources of uncertainty in the risk characterization for coriander oil

Key source of Uncertainty	Impact
Exposure	
There is a degree of uncertainty in extrapolating the dermal absorption data from linalool and citronellol to coriander oil; however, as linalool is a major constituent of coriander oil, and citronellol has similar physical-chemical properties to coriander oil, the dermal absorption of these compounds is expected to be similar.	+/-
Route-to-route extrapolation for coriander oil was carried out for inhalation and dermal scenarios in comparing to an effect level from oral studies.	+/-
Hazard	
There are no chronic or carcinogenicity animal studies for all routes of exposure.	+/-
There are no studies for dermal or inhalation exposure.	+/-
There are limited animal studies examining the repeated-dose toxicity of coriander oil for the relevant routes of exposure (i.e., dermal, oral, inhalation). Hazard data from the main components, linalool and geranyl acetate, were used to inform the health effects assessment, where applicable.	+/-
The composition of the coriander oil used in the 28-day repeated dose study in rats is unknown. Therefore, it is unknown whether the composition of the coriander oil used in the study is representative of the coriander oil Canadians are exposed to.	+/-

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

7.6 Rose oil

7.6.1 Sources and uses

Rose oil is a naturally occurring substance that is derived from steam distillation from flowers of various *Rosa* spp., primarily *R. damascena, R. centifolia and R. gallica* (Burdock 2010; FCC 2018).

Based on information submitted pursuant to a section 71 survey under CEPA (Canada 2012), there were no reports of import or manufacture above the reporting threshold of 100 kg for rose oil in 2011 (Environment Canada 2013).

Rose oil, *Rosa damascena* flower oil/extract, or rose flower oil is used in a wide range of cosmetic products in Canada. Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, general population exposure to rose oil may occur from the daily use of cosmetics where it is used in concentrations ranging from <0.1%-100%

in greater than 900 products (personal communication, emails from the Consumer Product Safety Directorate (CPSD), 2015; unreferenced). Some of the product types reported include body lotion, massage products, cleansers, fragrance, make-up, hair care, and bath products. The majority of products (>75%) contain rose oil at a concentration of 1% or less. In general, products with higher concentrations of rose oil are intended to be diluted prior to use (personal communication, emails from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

Rose oil is also listed as a fragrance ingredient used in consumer goods by the International Fragrance Association (IFRA 2017).

Information from the American Cleaning Institute's (ACI) website indicates potential use of rose oil as a fragrance in household cleaning products including all-purpose cleaners and dish and laundry care products (ACI 2017).

Rose oil has reported uses in food, including candy/chewing gum, baked goods and alcoholic beverages, dairy and gelatins/puddings, as a flavouring agent (Burdock 2010). Rose oil is listed in the US FDA Substances Added to Food inventory and in the Food Chemicals Codex as a flavouring agent (US FDA 2018; FCC 2018). No definitive information is available concerning the potential use of rose oil as a food flavouring agent in Canada however since the substance is known to be used as a food flavouring agent in the US, it is possible that the substance is present as a flavouring agent in foods sold in Canada.

Additional uses for rose oil are listed in Table 7.6-1.

Table 7.6-1. Additional uses in Canada for rose oil

Use	Details
Food flavouring[a]	Reported uses in candy/chewing gum, baked goods, alcoholic beverages, dairy and gelatins/puddings (Burdock 2010).
Natural Health Products Ingredients Database[b]	MI, NMI (fragrance in topical products, skin-conditioning agent)
Licensed Natural Health Products Database being present as a medicinal or non-medicinal ingredient in natural health products in Canada[b]	MI, NMI
Notified to be present in cosmetics, based on notifications submitted under the *Cosmetic Regulations* to Health Canada[c]	Skin and hair care products, fragrances, and deodorants
Formulant in pest control products registered in Canada[d]	Formulant

Abbreviations: MI, medicinal ingredient; NMI, non-medicinal ingredient.
[a] Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced
[b] Email communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced
[c] Email communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau; unreferenced
[d] Email communication from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau; unreferenced

7.6.2 **Potential to cause harm to human health**

7.6.2.1 Exposure assessment

In consideration of the low quantities (<100 kg) of the substance reported to be used in Canada (Environment Canada 2013), an impact on human health from exposure to rose oil from environmental media is not expected.

Dietary exposure of Canadians to rose oil when used as a food flavouring agent was estimated using the individual consumption of 9.18×10^{-5} mg/kg bw/day for the US population established in Fenaroli's Handbook of Flavor Ingredients (personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2017; unreferenced).

To evaluate the potential for exposure to rose oil from cosmetics applied by the dermal route, sentinel scenarios were selected based on a combination of use frequencies and reported concentrations of rose oil in these products. These scenarios represented the highest exposure, relative to other dermally applied cosmetics and natural health products based on identified products reported to contain the substance. Exposure to rose oil from the use of a body moisturizer, face moisturizer, and massage oil were considered to be the sentinel scenarios for products applied by the dermal route. These exposure scenarios are summarized in Appendix B (Tables B-1, B-2, and B-3).

The highest daily exposure to rose oil is expected to occur from the use of a body moisturizer and face moisturizer with reported concentrations of 1-3% rose oil. Systemic exposure by the dermal and inhalation routes for body moisturizer (assuming 20% dermal absorption for occluded skin) ranged from 7.08×10^{-1}-1.60 mg/kg bw/day for all age groups. As there was uncertainty with respect to whether body lotions at the upper concentration of 3% would be used on infants and toddlers, systemic exposure by the dermal and inhalation route for body lotion for infants and toddlers was also calculated at the lower concentration of 1%. Systemic exposure by the dermal and inhalation routes for infants and toddlers from a 1% body lotion ranged from 4.25×10^{-1} – 5.34×10^{-1} mg/kg bw/day. Systemic exposure by the dermal and inhalation routes for face moisturizer and massage oil (assuming 4% dermal absorption for unoccluded skin) ranged from 5.66×10^{-2} – 7.18×10^{-2} mg/kg bw/day for 12 to 19 years to adults and 4.55×10^{-2} - 3.74×10^{-1} mg/kg bw/day for adults to infants, respectively.

Depending on the source of rose oil, rose oil may contain methyl eugenol at a concentration of 0-3.3% (Tisserand and Young 2014). Methyl eugenol has been

assessed under the Chemicals Management Plan. It was concluded that methyl eugenol is a substance that may be entering the environment in a quantity of concentration or under conditions that constitute or may constitute a danger in Canada to human life or health (ECCC, HC 2010). In Canada and Europe, it is only permitted as a naturally occurring component in botanical extracts and is restricted to a maximum concentration of 0.01% in fine fragrances, 0.004% in eau de toilette, 0.002% in fragrance cream, 0.0002% in other leave-on product and oral hygiene products, and 0.001% rinse-off products (HC 2015; SCCS 2000).

Several natural health products containing *Rosa damascena* flower oil and rose essential oil as a non-medicinal ingredients were identified for topical use and therefore may result in exposure by the dermal route. Information on quantity of rose oil was not available for all products (email from Natural and Non-Prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, July 2015; unreferenced); exposure to rose oil from these natural health products is expected to be comparable or less than the highest estimates of dermal exposure to rose oil from use of cosmetics.

Exposure to rose oil by the inhalation route may occur from the use of certain cosmetics (e.g., spray perfume) and aromatherapy. Mean concentration on the day of exposure from a perfume containing 100% rose oil was determined to be 1.90×10^{-1} mg/m^3 (or systemic exposure ranging from 4.30×10^{-2} to 8.90×10^{-2} mg/kg bw/day) (adults to 5-year-olds) (full calculation parameters in Appendix-B, Table B-4). Inhalation exposure to rose oil from an aromatherapy diffuser was calculated using a Danish EPA health assessment document of chemical substances in essential oils and fragrance oils (Danish EPA 2008). Details of the scenario and exposure parameters are outlined in Appendix D (Tables D1-D2). Systemic exposures ranging from 6.00×10^{-2} – 1.50×10^{-1} mg/kg bw/day were derived for rose oil.

7.6.2.2 Health effects assessment

Rose oil has been classified by the US Food and Drug Administration (FDA as generally recognized as safe (GRAS) when used as food flavouring agent or adjuvant (US FDA 2017a).

No genotoxicity, carcinogenicity or chronic studies have been identified in the literature for rose oil.

Rose oil was evaluated in a series of short term toxicity studies.

In a repeated-dose study, male and female rats (10/per dose) were administered via gavage to 85 mg/kg (0.1 mL/kg) or 425 mg/kg (0.5 mL/kg) of rose oil diluted in 1 mL/kg of ethanol five times weekly for 30 days (Kirov et al. 1988a). Exposure to the highest dose (425 mg/kg dose) caused pronounced anemia (hemoglobin and hematocrit

reduction by 30-35%), increased spleen weights, as well as a decrease in body weight and relative liver, kidney and testes weights.

In a follow up study, the authors examined the effect of rose oil on lipid liver dystrophy (Kirov et al. 1988b). Male Wistar rats (20 per group) were administered orally to 1 mL/kg of 40% ethanol, 1mL/kg of 40% ethanol plus 0.01 mL/kg (8.5 mg/kg) rose oil or 1 mL/kg of 40% ethanol plus 0.05 mL/kg (42.5 mg/kg) rose oil for 6 months. The study showed that rose oil had a hepato-protective effect with decreased dystrophy and lipid infiltration and lowered glycogen levels in animals treated with rose oil (Kirov et al. 1988b).

In a developmental study (Kirov et al. 1988d), pregnant rats (20) were orally administered 0.1 mL/kg (85 mg/kg) of rose oil diluted in sunflower seed oil from GD1-21. Other rats were also orally administered a single dose of either undiluted 0.35 mL/kg (305 mg/kg) or 1.75 mL/kg (1488 mg/kg) rose oil (corresponding to 1/2 and 1/10 of the LD50) on GD 5, 7, 9, 11 or 13. No pre or post-implantation loss, or fetal malformations were observed. There was however an increased incidence in delayed ossification of the skull (widened fontanelles and cranial sutures) in animals treated with rose oil at 305 or 1488 mg/kg on days 7 and 9. No further details regarding the extent and occurrence of the delayed skull ossification were available. In this study, as no statistical analysis was presented, it was not possible to establish a dose response relationship.

In order to further inform the risk assessment, the hazard information available for the main components of rose oil, citronellol (15-48%), and geraniol (6-32%) were considered. Based on available information, health effects of concern were not identified for both components. Further information on the health effects of geraniol and citronellol are provided in the Potential to cause harm to human health sections for palmarosa oil and geranium oil, respectively (section 7.2.2 and section 7.3.2).

7.6.2.3 Characterization of risk to human health

A NOAEL of 85 mg/kg was identified for rose oil from a 30-day repeated dose rat study. The effect level is based on a significant and dose related decrease in hematocrit and hemoglobin values along with a concomitant significant increase in spleen weights (Kirov et al. 1988a). No hazard data exists for rose oil via the dermal or inhalation route of exposure. In the present assessment, the oral NOAEL of 85 mg/kg bw/day was used for characterization of risk along with route-to-route extrapolation. It was assumed that absorption of rose oil by inhalation was equivalent to absorption by the oral route after accounting for the amount absorbed dermally.

Table 7.6-2. Relevant exposure estimates, critical effect levels and resulting margins of exposure, for rose oil

Exposure Scenario[a]	Systemic Exposure (mg/kg bw/day)	MOE[b]
Food flavouring (dietary intake)	9.18×10^{-5} (6 months and above)	925 926 (6 months and above)
Systemic exposure by the dermal and inhalation routes from body lotion (3%)[c]	1.27-1.60 (toddler-infant) 7.03×10^{-1} – 8.46×10^{-1} (all other age groups)	**53 - 67** (infant–toddler) 100 - 121 (all other age groups)
Systemic exposure by the dermal and inhalation routes from body lotion (1%)[c]	4.25×10^{-1} – 5.34×10^{-1} (toddler-infant)	159 - 200 (infant–toddler)
Systemic exposure by the dermal and inhalation routes from massage oil (5 drops from 30% upper concentration) [d]	4.55×10^{-2} – 3.74×10^{-1} (adult-infant)	227 - 1 870 (infant–adult)
Systemic exposure by the dermal and inhalation routes from face moisturizer (3%) [d]	5.66×10^{-2} – 7.18×10^{-2} (adult-12 to 19 yrs)	1 184 - 1 501 (12 to 19 yrs-adult)
Systemic exposure by the inhalation route from fragrance product (100%)	4.30×10^{-2} – 8.80×10^{-2} (adult-5 to 11 yrs)	966 - 1 977 (5 to 11 yrs-adult)
Systemic exposure by the inhalation route from aromatherapy [e] (1.45 mg/m^3)	6.00×10^{-2} – 1.50×10^{-1} (all age groups)	567 - 1 417 (all age groups)

[a] Exposure scenario parameters and calculations for rose oil outlined in Appendix B
[b] Margin of exposure calculated using a critical effect level (NOAEL = 85 mg/kg bw/day) for rose oil based on decreased hematocrit levels and increased spleen weight from a 30 day oral study in rats.
[c] Assuming dermal absorption of 20% (occluded)
[d] Assuming dermal absorption of 4% (unoccluded)
[e] Refer to Appendix D for Aromatherapy Scenario details

The MOE between the critical effect level and the estimate of daily exposure to rose oil from a 3% body moisturizer for infants and toddlers ranged from 53 to 67, which is considered potentially inadequate to account for uncertainties in the health effects and exposure databases. It should be noted; however, that there is uncertainty as to whether body lotions at the upper concentration of 3% would be used on a daily basis on infants and toddlers. Therefore, the MOE for the lower concentration of a 1% body lotion was also calculated for infants and toddlers, which resulted in a MOE ranging from 159 to 200, which is considered adequate to account for uncertainties in the database.

For all other exposure scenarios, the MOE between the critical effect level and the estimate of exposure ranged from 100 to 925 926, which is considered adequate to account for uncertainties in the health effects and exposure databases.

7.6.2.4 Uncertainties in evaluation of risk to human health

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

Table 7.6-3. Sources of uncertainty in the risk characterization for rose oil

Key source of Uncertainty	Impact
Exposure	
There is a degree of uncertainty in extrapolating the dermal absorption data from linalool and citronellol to rose oil; however, as all the acyclic/monocyclic/bicyclic monoterpenes and constituents thereof have similar physical-chemical properties, the dermal absorption of these compounds is expected to be similar.	+/-
There is a degree of uncertainty as to whether body lotion at the upper concentration of 3% rose oil would be used on a daily basis on all subpopulations, such as infants and toddlers.	+
Route-to-route extrapolation for rose oil was carried out for inhalation and dermal scenarios in comparing to an effect level from oral studies.	+/-
Hazard	
There are no chronic, genotoxicity or carcinogenicity animal studies for all routes of exposure.	-
The composition of the rose oil used in the 30-day repeated dose rat study is unknown. Therefore, it is unknown whether the composition of the rose oil used in the study is representative of the rose oil Canadians are exposed to.	+/-

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

7.7 Lemongrass oil

7.7.1 Sources and uses

Lemongrass oil is a naturally occurring substance that is derived from steam distillation of *Cymbopogon citratus or Cymbopogon flexuosus* species of grass native to India, Sri Lanka, Burma and Thailand (Burdock 2010; Chowdhury 2010; Tisserand and Young 2014). It is commonly known as either East or West Indian lemongrass depending on the species it originates from; West Indian being of *Cymbopogon citratus* species and East Indian being of *Cymbopogon flexuosus* species (Tisserand and Young 2014).

Based on information submitted pursuant to a section 71 survey under CEPA (Canada 2012), there were no reports of import or manufacture above the reporting threshold of 100 kg for lemongrass oil in 2011 (Environment Canada 2013).

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, Lemongrass oil, *Cymbopogon Schoenanthus* Oil, Cymbopogon flexuosus, *Cymbopogon Citratus* Leaf Oil is used in greater than 700 cosmetic products in Canada with concentrations ranging from <0.1%-100% (personal communication, emails from the Consumer Product Safety Directorate, 2017; unreferenced). Some of the product types reported include body lotion, massage products, cleansers, fragrance, make-up, hair care, and bath products. The majority of products (>65%) contain lemongrass oil at a concentration range of 1% or less. In general, products with higher concentrations of lemongrass oil are intended to be diluted prior to use (personal communication, emails from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

Lemongrass oil is also listed as a fragrance ingredient used in consumer goods by the International Fragrance Association (IFRA 2017).

Information from the American Cleaning Institute's (ACI) website indicates potential use of lemongrass oil as a fragrance in household cleaning products including all-purpose cleaners and dish and laundry care products (ACI 2017).

Lemongrass has a long history of use as an herb in Asian cuisine, and is commonly used in soups, curries and teas (Olorunnisola et al. 2014). It also has reported uses in food including alcoholic and non-alcoholic beverages, baked goods, fats/oils, frozen dairy, gelatins/puddings, meat products and candy/chewing gum (Burdock 2010). Lemongrass oil is listed in the US FDA Substances Added to Food inventory and in the Food Chemicals Codex as a flavouring agent (US FDA 2018; FCC 2018). No definitive information is available concerning the potential use of lemongrass oil as a food flavouring agent in Canada however since the substance is known to be used as a food flavouring agent in the US, it is possible that the substance is present as a flavouring agent in foods sold in Canada.

Additional uses for lemongrass oil are listed in Table 7.7-1.

Table 7.7-1. Additional uses in Canada for lemongrass oil

Use	Details
Food flavouring[a]	Reported uses in alcoholic and non-alcoholic beverages, baked goods, fats/oils, frozen dairy, gelatins/puddings, meat products and candy/chewing gum (Burdock 2010).
Incidental additives[a]	Component in sanitizer for food contact surfaces.
Drug Products Database[b]	NMI

Use	Details
	(disinfectant)
Natural Health Products Ingredients Database[c]	MI, NMI (Cymbopogon Flexuosus oil as masking agent, Cymbopogon Schoenanthus oil as fragrance, East Indian lemongrass essential oil as flavor enhancer)
Licensed Natural Health Products Database being present as a medicinal or non-medicinal ingredient in natural health products in Canada[c]	MI, NMI
Notified to be present in cosmetics, based on notifications submitted under the *Cosmetic Regulations* to Health Canada[d]	Skin and hair care products, fragrances, and deodorants.
Formulant in pest control products registered in Canada[e]	Active ingredient and formulant

Abbreviations: MI, medicinal ingredient; NMI, non-medicinal ingredient.

[a] Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced; Burdock 2010.

[b] Email communication from Therapeutic Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[c] Email communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[d] Email communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[e] Email communication from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau; unreferenced

7.7.2 Potential to cause harm to human health

7.7.2.1 Exposure assessment

In consideration of the low quantities (<100 kg) of the substance reported to be used in Canada (Environment Canada 2013), an impact on human health from exposure to lemongrass oil from environmental media is not expected.

The per capita intake (PCI) of lemongrass oil from its use as a food flavouring agent was estimated to be 19 µg/person per day for the US population based on JECFA's safety evaluation of natural flavouring complexes at its 61st meeting (WHO 2004b) (July 2017 email from the Food Directorate, Health Canada to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced) (personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2017; unreferenced). This in turn yields an estimated intake of 2.68×10^{-4} mg/kg bw/day (based on 70.9 kg adult body weight).

Lemongrass oil has also been identified as a potential incidental food additive from its use as a component in sanitizer for food contact surfaces (which are not rinsed with potable water after its use). However, the potential for exposure from this source is

negligible as any food contact surface is to be drained and dried thoroughly after use of the product (personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2017; unreferenced).

To evaluate the potential for exposure to lemongrass oil from cosmetics, sentinel scenarios were selected based on a combination of use frequencies and reported concentrations of lemongrass oil in these products. These scenarios represented the highest exposure by dermal application, relative to other dermally applied cosmetics and natural health products based on identified products reported to contain the substance. Exposure to lemongrass oil from the use of a body moisturizer and massage oil were considered to be the sentinel scenarios to estimate daily exposure by the dermal route of administration. This data is summarized in Appendix C (Tables C-1, C-2, and C-3).

The highest daily exposure by the dermal route of administration to lemongrass oil is expected to occur from the use of a body moisturizer with a reported upper concentration of 5% lemongrass oil and massage oil. Inhalation exposure from body moisturizer was estimated with mean concentration on the day of exposure ranging from 1.60×10^{-2} - 5.90×10^{-2} mg/m^3 and systemic exposures by the dermal and inhalation routes ranging from 1.19 to 2.67 mg/kg bw/day (adult to infant). For massage oil, inhalation exposure ranged from 8.00×10^{-2} – 8.20×10^{-2} mg/m^3 and systemic exposures by the dermal and inhalation routes ranged from 1.20×10^{-1} – 9.82×10^{-1} mg/kg bw/day (adult to infant).

Exposure to lemongrass by the inhalation route may result from the use of certain cosmetics (e.g., spray perfume) and aromatherapy. Mean concentration on the day of exposure from a perfume containing 30% lemongrass oil was determined to be 5.80×10^{-2} mg/m^3 (adults to 5 year-olds) (full calculation parameters in Appendix-C, Table C-4). Exposure to lemongrass oil by the inhalation route from an aromatherapy diffuser was calculated using a Danish EPA health assessment document of chemical substances in essential oils and fragrance oils (Danish EPA 2008). This scenario was set up based on the description of use patterns and an average air concentration of 1.45 mg/m^3 was measured in 4 hours of exposure. Details of the scenario and exposure parameters are outlined in Appendix D (Tables D1-D3).

Several disinfectant products (wipes/spray) were reported as containing lemongrass oil as a non-medicinal ingredient (concentration ranging from 0.05-1%) (email from Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, Jan 2017; unreferenced). Information from the American Cleaning Institute's (ACI) website indicates potential use of lemongrass oil as a fragrance in household cleaning products including all-purpose cleaners, and dish and laundry care products (ACI 2018). To assess potential exposure to lemongrass oil from its use in household cleaning products, the use of lemongrass oil in an all-purpose floor cleaner was assessed. It was assumed that lemongrass oil would be present at a maximum concentration of 1% as it is typically used as a fragrance in cleaning products, and this is the suggested upper limit concentration of fragrances in household cleaning

products (Fleurarome Limitee 2016). Systemic exposure estimates of 2.52 x 10^{-3} mg/kg bw/day and 5.66 x 10^{-3} mg/kg bw/day were calculated for adults and toddlers using the exposure parameters outlined in Appendix D (Table D4). The use of lemongrass oil in a floor cleaner was expected to result in the greatest potential exposure from its use in cleaning products. Details on the scenario and exposure parameters are outlined in Appendix C (Table C4-C5).

A natural health product administered by the oral route containing 0.12 mg/tablet of lemongrass oil as non-medicinal ingredient was listed in a nutritional supplement (personal communication with NNHPD, Jan 2018, unreferenced). The highest systemic exposure from this product was calculated to be 3.39 x 10^{-3} mg/kg bw/day (used by adults only).

7.7.2.2 Health effects assessment

Hazard assessment of lemongrass oil

Evaluation of lemongrass oil by the Joint FAO/WHO Expert Committee on Food Additives has concluded that it does not present a safety concern as a food flavouring agent based on estimated levels of intake (WHO 2004b). Lemongrass oil has also been classified by the US Food and Drug Administration (US FDA) as generally recognized as safe (GRAS) when used as a food flavouring agent or adjuvant (US FDA 2017a).

Limited toxicological information is available for lemongrass oil.

A number of short-term oral studies evaluating lemongrass extract, as opposed to lemongrass oil, were identified in the literature. The extracts of lemongrass are expected to contain the same main components as the oil (Mu'azu et al. 2016, Schaneberg and Khan 2002) and consequently data from these studies was considered relevant for health effect characterization of lemongrass oil.

In repeated dose studies, the effects of oral administration of extracts of lemongrass were investigated in rats and mice. Wistar rats were administered orally via gavage for 28 days to 0, 250, 500 and 1 000 mg/kg bw/day of either the aqueous or ethanol extract of lemongrass (Tarkang et al. 2012). In a 90-day study, rats were orally administered the same concentrations but of the aqueous extract only. No significant changes in body or organ weight were noted following exposure to either extract. The group of 1 000 mg/kg bw/day of both the aqueous extract for 90 days and the ethanol extract for 28 days showed increased levels of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) which was indicative of liver damage. Moreover, the histopathological examination revealed vascular congestion and scarring in the liver. In addition to the liver effects, examinations also revealed mild tubular distortion in the kidney of rats treated with 1 000 mg/kg bw/day of the ethanol extract for 28 days.

In a similar study, an oral administration of 1, 10 or 100 mg/kg bw/day lemongrass oil by gavage to male mice (7-8 animals per group) for 21 days resulted in no significant changes in body/organ weight, gross pathology, histology, urinalysis or clinical biochemistry (Costa et al. 2011). Rats were administered orally to higher maximum concentrations of lemongrass oil (up to 3 000 mg/kg bw/day) for 14 days and demonstrated adverse effects, including atrophy of the stomach mucosa, infiltration of inflammatory cells and hepatocyte necrosis, at 1 500 mg/kg bw/day or higher dose (Fandohan et al. 2008). Some changes in hematological parameters and enzymes indicative of kidney function were observed in a 30-day oral study in male Wistar rats administered 0 to 5 000 mg/kg bw/day lemongrass (ethanol extract). However, no dose-response was identified and the parameters were considered to be within normal biological and laboratory limits (Ademuyiwa et al. 2016).

Human lymphocytes exposed to lemongrass oil (in vitro) caused DNA damage in a comet assay or DNA diffusion assay at 100 µg/mL or higher concentration (Sinha et al. 2014). Conversely, in vivo exposure of male mice to 100 mg/kg bw/day of lemongrass oil for 21 days was negative for DNA damage in the comet assay (Costa et al. 2011).

No chronic, reproductive/developmental toxicity or carcinogenicity studies have been identified in the literature for lemongrass oil. In order to further inform the risk assessment, the hazard information available for the main component of lemongrass oil, total citral (67-92%), beta-myrcene (6-27%), geranyl acetate (12%), and citronellol (0-24%) have been considered.

Hazard assessment of main components

Citral

Evaluation of citral by the Joint FAO/WHO Expert Committee on Food Additives has concluded that it does not present a safety concern as a food flavouring agent based on estimated levels of intake (WHO 2004b).

Citral was not reported as a reproductive or a developmental toxicant (MHW, Japan 2002). Male and female rats were administered orally to 40, 200 or 1 000 mg/kg bw/day of citral by gavage for approximately 46 days prior to and through mating and gestation. The highest dose (1 000 mg/kg bw/day), caused decreases in body weight and food consumption, as well as histopathological effects in the forestomach in dams, while pups experienced decreased body weight. Based on these results, a NOAEL of 200 mg/kg bw/day was determined for maternal toxicity.

In a prenatal developmental toxicity study, rabbits (25/dose) were administered 20, 60, or 200 mg/kg bw/day of citral by gavage during GD 6-28. Dams in the 200 mg/kg bw/day dose group showed decrease in body weight and weight gain, reduced food consumption, mortality (2 rabbits) and abortion (1 rabbit). In addition, a litter of pups from a dam in the 200 mg/kg bw/day developed external malformations due to severe maternal toxicity (ECHA 2016). However, of note is that New Zealand white rabbits are

particularly difficult to gavage and evidence of stomach irritation (severe reddening of the stomach mucosa) was observed in rabbits that died in the high dose group. Based on these results, a NOAEL of 60 mg/kg bw/day was noted for maternal toxicity. It is possible that gavage-related issues might also be responsible for the difference in NOAELs between the previous study and this one (i.e., 200 mg/kg bw/day versus 60 mg/kg bw/day).

In an inhalation study, pregnant rats were exposed (whole body) to 10, 34, 68 ppm citral for 6 hrs/d from GD 6 to15 (Gaworski et al. 1992). The 10 and 34 ppm doses were administered as vapours while 68 ppm dose was a combination of aerosol and vapour. Maternal effects observed at 68 ppm included mortality (1 female on day 10 of gestation), abortion (1 female on day 17 of gestation), reduced body weights, ocular opacity, breathing difficulty, nasal discharge and salivation and were associated with severe respiratory tract irritation. Changes in body weight and signs of toxicity reversed up on cessation of exposure. At 68 ppm, in the presence of maternal toxicity, the fetus showed a non-significant decrease in body weight and hypoplastic (small size) bones. No maternal or offspring effects were noted at the two lower doses; therefore, the adjusted NOAEC was calculated to be 53.75 mg/m^3 (34 ppm or 215 mg/m^3 adjusted for 6 hours of exposure per day) based on maternal toxicity at 68 ppm ($LOAEC_{adj}$ = 105.75 mg/m^3, based on a LOAEL of 423 mg/m^3 adjusted for 6 hours exposure per day). No developmental toxicity was observed in the absence of maternal toxicity (Gaworski et al. 1992).

Citral was reviewed previously in an OECD SIDS initial assessment report (OECD/SIDS 2001). This report concluded that, based on weight of evidence, citral was not considered to pose a genotoxic hazard. In addition, several short term repeated dose studies in rodents showed no adverse effects at exposures less than 1 000 mg/kg bw/day.

In a two-year feeding study in rats and mice, citral did not cause carcinogenicity in male and female rats or in male mice (NTP 2001). There was equivocal evidence of malignant lymphoma in female mice. Lymphomas in treated female mice occurred with a positive trend and were significantly higher than controls; however, incidences were within NTP historical control values and could not clearly be related to citral administration (Ress et al. 2003).

Beta-Myrcene

The International Agency for Research on Cancer (IARC) considers beta-myrcene as a medium priority agent to be evaluated and classifies it in the group 2B: possibly carcinogenic to humans (IARC 2014). The office of Environmental Health Hazard Assessment (OEHHA) is adding beta-myrcene to the list of chemicals known to the state to cause cancer for purposes of Proposition 65 (OEHHA 2018). However, the European Food Safety Authority (EFSA) had deemed beta-myrcene not to pose a safety concern when used as flavouring substances at estimated levels of intake (EFSA 2015a).

Male and female F344/N rats (n = 10/sex/doses) were administered 0, 250, 500, 1 000, 2 000 or 4 000 mg/kg bw/day beta-myrcene by gavage for 5 days per week for 14 weeks (NTP 2010). All study rats (males and females) in the 4000 mg/kg bw/day groups died during the first two weeks. Mean body weights were significantly decreased in male rats administered 500 mg/kg bw/day or greater. Kidney and liver weights of both sexes were significantly greater at all doses. The thymus weight of male rats was significantly decreased in a dose-related way starting at 500 mg/kg bw/day. Chronic progressive nephropathy, alpha-2u-globulin nephropathy and renal tubule degeneration were increased in all dosed groups in both sexes. The incidence of olfactory epithelium degeneration in 2 000 mg/kg bw/day male and female rats was significantly increased. Authors determined a LOAEL at 250 mg/kg bw/day based on these results (NTP 2010).

Male and female B6C3F1 mice (n = 10/sex/doses) were orally administrated with 0, 250, 500, 1 000, 2 000 or 4 000 mg/kg bw/day beta-myrcene by gavage for 5 days per week for 14 weeks (NTP 2010). Similar to the rats, 4 000 and 2 000 mg/kg bw/day were lethal for all animals. The kidney weights of 1 000 mg/kg bw/day females and the liver weights of females administered 500 or 1 000 mg/kg bw/day were significantly increased. No significant increases in frequency of micronucleated normochromatic erythrocytes were observed in male or female mice. Beta-myrcene is not considered to be genotoxic at those doses. Authors determined a NOAEL of 250 mg/kg bw/day based on the absence of adverse effect and a LOAEL of 500 mg/kg bw/day based on the significant increase of liver weight and the significant decrease of body weight (NTP 2010).

At the request of the European Food Safety Authority (EFSA) for additional toxicological data on beta-myrcene as a flavouring agent, male and female rats (10/sex/group) were fed a diet containing 0, 700, 2 100, or 4 200 ppm (meaning 0, 20.4, 58.8, or 115.2 mg/kg bw/day for males and 0, 50, 150, or 300 mg/kg bw/day for females) beta-myrcene for a 90-day study (Bastaki et al. 2018). Adverse effects were not observed (Bataski et al. 2018). Authors concluded a NOAEL at 115 and 136 mg/kg bw/day based on both high doses for males and females, respectively (Bastaki et al. 2018).

Wistar rats (15 males/45 females/dose) were administered 0, 100, 300 or 500 mg/kg bw/day beta-myrcene by gavage for 91 days prior and during mating for males and for 21 days prior and during mating, during pregnancy and lactation until postnatal 21-day (91 days in total) (Paumgartten et al. 1998). No deaths were induced and no other signs of toxicity were apparent in male rats. A significant increase of liver and kidney weights in males was found in the 500 mg/kg bw/day group in the absence of morphological alterations. The 500 mg/kg bw/day dose produced a significant increase in the resorption rate, a decrease in the number of live fetuses and an increase in the frequency of skeletal malformations as fused zygomatic, dislocated sternum and lumbar extra ribs. Based on these data, a NOAEL for reproductive toxicology was set at 300 mg/kg bw/day by authors (Paumgartten et al. 1998).

Pregnant female rats were administered 0, 250, 500, 1 000 or 1 500 mg/kg bw/day beta-myrcene by gavage from pregnancy day 15 to the weaning day (postnatal day 21)

(Delgado et al. 1993b). The death of five dams within the first week of treatment and a decrease in weight at pregnancy term, which persisted after delivery, suggested maternal toxicity at 1500 mg/kg bw/day. The ratio of females mated that gave birth was significantly lower at 1 000 and 1 500 mg/kg bw/day. A significant decrease in pup weight as well as a significant increase in pup mortality during lactation at 500 mg/kg bw/day and above was observed. Based on these results, authors derived a NOAEL for developmental toxicity at 250 mg/kg bw/day (Delgado et al. 1993b).

Wistar rats were administered 0, 250, 500 and 1200 mg/kg bw/day beta-myrcene by gavage from gestation days 6 to 15 (Delgado et al. 1993a). Adverse effects were not seen with 250 and 500 mg/kg bw/day. Decreased weight gain during the first days of treatment and one death in treated dams suggested maternal toxicity at 1 200 mg/kg bw/day. A significant decrease in implantation sites, the number of live fetuses, fetus weight and significant delayed ossification in skull bones, caudal vertebrae, forelimbs and hind limbs. Based on these results, authors set a NOAEL at 500 mg/kg bw/day for maternal toxicity and foetotoxicity (Delgado et al. 1993a).

The rat popliteal lymph node assay (PLNA) was positive for 5 mg/paw β-myrcene (Friedrich et al. 2007). A secondary PLNA, a T-cell priming test showed that β-myrcene was negative in the secondary assay, indicating that beta-myrcene induced an immunostimulatory response due to their irritant properties (Friedrich et al. 2007).

Eye irritation was examined in a study conducted in compliance with OECD guideline 405 by administering 0.1 mL of undiluted myrcene in the eyes of New Zealand White rabbit males (ECHA 2009). No washing was done and the animals were observed for a period of 8 days. After 1 hour, moderate redness of the conjunctivae associated with slight to severe chemosis resulted in all treated animals. However, the irritation resolved within 8 days (ECHA 2009).

A study was conducted in vitro with human epidermis model EPISKIN to assess skin irritation potential (ECHA 2009). A volume of 10µL of undiluted beta-myrcene was applied directly on epidermis for 15 min on 3 samples and the percentage of cellular viability was evaluated. The positive control and the beta-myrcene treatment resulted in a value of cell viability of 18.7% and 25.9%, respectively. Since cell viability was below 50%, beta-myrcene is considered to be irritating (ECHA 2009).

With respect to skin sensitization assay, a negative response was observed in a local lymph node assay (LLNA) conducted in CBA/J female mice (4/group) treated with 25 µL of 2.5, 5, 10, 25 or 50% beta-myrcene in acetone/olive oil (4:1 v/v) vehicle for 3 consecutive days (ECHA 2009). The SI was lower than 3 in all treated groups and no clinical signs or mortality were observed during the study (ECHA 2009).

All in vitro genotoxicity studies – Ames, chromosomal aberration study and a mouse lymphoma assay, did not show any evidence of genotoxicity activity. Beta-myrcene is not considered to be genotoxic (ECHA 2009).

In a 2-year study conducted by the National Toxicology Program (NTP), F344/N rats received by gavage 0, 250, 500 or 1 000 mg/kg bw/day beta-myrcene 5 days per week (NTP 2010). All males from 1 000 mg/kg bw/day died before the end of the study due to high renal toxicity. The frequency of renal tubule nephrosis was significantly increased in all dosed groups of both sexes except in 250 mg/kg females. A significant increase in nephropathy occurred in dosed females. Nephrosis was a unique lesion in the 2-year study of beta-myrcene in rats and was more severe in males than in females. The pathogenesis of this lesion is unknown but might be a response to a repeated renal tubule epithelial cell injury and might be linked to the neoplasia (NTP 2010). Authors concluded that under the conditions of this 2-year gavage study, there was clear evidence of carcinogenic activity of beta-myrcene in male rats and equivocal evidence in females (NTP 2010).

In a 2-year study conducted by the National Toxicology Program (NTP), B6C3F1 mice received by gavage 0, 250, 500 or 1 000 mg/kg bw/day beta-myrcene 5 days per week (NTP 2010). The survival rate was significantly decreased at 1000 mg/kg bw/day for both sexes. Mean body weight of 1 000 mg/kg bw/day males and females and 500 mg/kg bw/day females were less than controls after weeks 11 and 17 weeks. Incidences of hepatocellular adenoma, carcinoma and hepatoblastoma in the 500 mg/kg bw/day group and only hepatocellular adenoma for 250 mg/kg bw/day were significantly greater than controls. A significantly increased incidence of lymphoid follicle atrophy occurred in the spleen of 500 mg/kg bw/day females, and dose related increases in severity were found in males and females. In females, significantly increased incidences of inflammation and epithelial hyperplasia of the forestomach occurred in the 500 mg/kg bw/day group. The inflammation was mainly chronic in duration (NTP 2010). Authors concluded that, under the conditions of the 2-year gavage study, there was clear evidence of carcinogenic activity of beta-myrcene in male mice and equivocal evidence in females (NTP 2010).

Geranyl Acetate

Available studies did not show the genotoxicity or carcinogenicity potential of geranyl acetate in experimental animals (US EPA 2009). In addition, adverse effects reported in repeated dose studies in rodents were observed only following exposure to 1 400 mg/kg bw/day or higher doses of this substance (US EPA 2009). Further information on the health effects of geranyl acetate are provided in the Potential to cause harm to human health section of this document for palmarosa oil (Section 7.2.2).

Citronellol and Geraniol

Based on available information, health effects of concern were not identified for both components. Further information on the health effects of citronellol and geraniol are provided in the Potential to cause harm to human health section of this document for geranium oil (Section 7.3.2) and palmarosa oil (Section 7.2.2), respectively.

7.7.2.3 Characterization of risk to human health

Oral/Dermal:

Even though toxicity data was available for beta-mycene, beta-mycene is only present in lemongrass oil at concentrations ranging from 6-27%; therefore, the toxicity data for lemongrass oil/extract and citral were considered more representative of lemongrass oil.

The oral administration of citral during development in rabbits resulted in the lowest NOAEL (ECHA 2016). Although citral was not teratogenic, maternal effects including decreased body weight and weight gain, reduced food consumption, mortality and abortion were observed at 200 mg/kg bw/day. In contrast, rats exposed to citral in a reproductive and developmental study showed maternal effects at a much higher dose of 1 000 mg/kg bw/day (MHW, Japan 2002), indicating species-specific effects. Importantly, New Zealand white rabbits are particularly difficult to gavage and evidence of stomach irritation (severe reddening of the stomach mucosa) was observed in rabbits that died in the high dose group. It is suggested that the administration of chemical via gavage might be partly responsible for the difference in the NOAELs.

Recognizing the difference in the magnitude of the NOAELs between the rat and rabbit studies and considering that good quality data exists for lemongrass extract in rat, the rabbit study was not recommended for use for the oral point of departure. Rather, the critical effect level recommended for the oral route is a NOAEL of 500 mg/kg bw/day identified in a 90-day study of lemongrass extract in rats. The effect level is based on increased levels of the liver enzymes ALT and ALP, as well as on vascular congestion and scarring in the liver at 1 000 mg/kg bw/day (Tarkang et al. 2012).

No health effects data were identified for lemongrass oil/extract or citral by the dermal route of exposure. Therefore, an oral NOAEL of 500 mg/kg bw/day as identified above was used for characterization of risk along with route-to-route extrapolation.

Inhalation:

No health effects data exists for lemongrass oil/extract via the inhalation route. Consequently, inhalation data for total citral, the main component comprising 67-92% of lemongrass was considered for this point of departure. The uncertainty in using data from a component was expected to be lower than the uncertainty encountered in conducting route-to-route extrapolation. The critical effect level was a NOAEC of 215 mg/m^3 (34 ppm) (adjusted to 53.75 mg/m^3 to account for the 6hr/day exposure) as identified in a developmental toxicity study of citral in rats. The effect level was based on mortality and abortion in dams observed at 423 mg/m^3 (68 ppm) (Gaworski et al. 1992).

Since it is unknown whether the toxic effect observed by the inhalation route was the result of a single exposure or repeated exposure events, and there was also severe respiratory tract irritation observed in the study, it was considered appropriate to

compare air concentrations associated with the inhalation exposure scenario directly to the adjusted NOAEC from the inhalation toxicity study of 53.75 mg/m^3.

Given that the majority of lemongrass oil is comprised of citral, the toxicity of citral by the inhalation route was considered to be equivalent to lemongrass extract.

Table 7.7-2. Relevant exposure estimates, critical effect levels and resulting margins of exposure, for lemongrass oil

Exposure Scenario[a]	**Exposure**	**MOE[b]**
Food flavouring (dietary intake)	2.68 × 10^{-4} mg/kg bw/day (adult)	1 865 671 (adult)
Exposure by the inhalation route from body lotion (5%)	1.6 x 10^{-2} – 5.9 x 10^{-2} mg/m^3 (24 hrs) (all age groups)	911 - 3 359 (all age groups)
Systemic exposure by the dermal and inhalation routes from body lotion (5%)[c]	1.19 – 2.67 mg/kg bw/day (all age groups)	187 - 422 (all age groups)
Exposure by the inhalation route from massage oil (4 drops from 100% upper concentration)	8.00 x 10^{-2} – 8.20 x 10^{-2} mg/m^3 (all age groups)	655 - 672 (all age groups)
Systemic exposure by the dermal and inhalation routes from massage oil scenario (4 drops from 100% upper concentration)[d]	1.20 x 10^{-1} – 9.82 x 10^{-1} mg/kg bw/day (adult-infant)	509 - 4 176 (infant–adult)
Exposure by the inhalation route from fragrance product (30%)	5.80 x 10^{-2} mg/m^3 (adult-5 to 11 yrs)	927 (5 to 11 years-adult)
Exposure by the inhalation route from aromatherapy[e] (1.45 mg/m^3) (4 hr)	2.40 x 10^{-1} mg/m^3 (24 hr amortized) (all age groups)	224 (all age groups)
Systemic exposure by the dermal and inhalation routes from mixing, loading, and application of an all-purpose floor cleaner (1%)[d]	2.52 x 10^{-3} mg/kg bw/day (adult)	198 400 (adult)
Exposure by the inhalation route from mixing, loading, and application of an all-purpose floor cleaner (1%)	1.90 x 10^{-3} mg/m^3 (24 hr) (adult)	28 300 (adult)
Systemic exposure by the dermal, inhalation and incidental oral route from contacting cleaned floors (1%)[d]	5.66 x 10^{-3} mg/kg bw/day (toddler)	88 390 (toddler)

Exposure Scenario[a]	Exposure	MOE[b]
Systemic exposure by the oral route from a nutritional supplement (NMI) (0.12mg/Tablet)	3.39×10^{-3} mg/kg bw/day (adult)	147 492 (adult)

[a] Exposure scenario parameters and calculations for lemongrass oil outlined in Appendix C
[b] For dermal and combined exposure scenarios, the critical effect level (NOAEL = 500 mg/kg bw/day) is based on increased levels of ALT, ALP, vascular congestion and scarring in the liver from a 90 day oral study of lemongrass extract in rats. For inhalation scenarios, the critical effect level ($NOAEC_{adj}$ = 53.75 mg/m^3) is based on mortality, abortion in dams from the inhalation developmental toxicity study of citral in rats.
[c] Assuming dermal absorption of 20% (occluded)
[d] Assuming dermal absorption of 4% (unoccluded)
[e] Refer to Appendix D for Aromatherapy Scenario details

The margin of exposure between the critical effect level and the estimate of exposure was considered adequate to account for uncertainties in the health effects and exposure databases.

7.7.2.4 Uncertainties in evaluation of risk to human health

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

Table 7.7-3. Sources of uncertainty in the risk characterization for lemongrass oil

Key source of Uncertainty	Impact
Exposure	
There is a degree of uncertainty in extrapolating the dermal absorption data from linalool and citronellol to lemongrass oil; however, as all the acyclic/monocyclic/bicyclic monoterpenes and constituents thereof have similar physical-chemical properties, the dermal absorption of these compounds is expected to be similar.	+/-
Route-to-route extrapolation for lemongrass oil was carried out for dermal scenarios in comparing to an effect level from an oral study.	+/-
The composition of the main components in lemongrass oil differs depending on the origin of the plant, its species, temperature, soil, and geography. Therefore, the composition of the lemongrass oil present in products available to Canadians is unknown, which represents an uncertainity in the assesment.	+/-
Hazard	
There are no chronic, reproductive/developmental, genotoxicity or carcinogenicity animal studies for all routes of exposure.	+/-
There are no studies for dermal or inhalation exposure.	+/-
There are limited animal studies examining the repeated-dose toxicity of lemongrass oil for the relevant routes of exposure (i.e., dermal, oral, inhalation). Hazard data from the main component, citral, was used to inform the health effects assessment, where applicable.	+/-

Key source of Uncertainty	Impact
The compostition of lemongrass extract in the 90-day study in rats is unknown. Therefore, it is unknown whether the composition of lemongrass extract is representative of the lemongrass oil Canadians are exposed to.	+/-

+ = 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. Monocyclic and bicyclic monoterpenes

8.1 Sweet orange oil

8.1.1 Sources and uses

Sweet orange oil is a naturally occurring substance obtained by distillation from the fresh peel or juice of the fruit of *Citrus sinensis* found predominantly in Asia, the Mediterranean, North Africa and the US (Burdock 2010).

Based on information submitted pursuant to a section 71 survey under CEPA (Canada 2012), a total of 2568 kg of sweet orange oil were manufactured in Canada in 2011 (Environment Canada 2013). A total of 36 576.37 kg of sweet orange oil was imported into Canada during the same calendar year (Environment Canada 2013).

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, sweet orange oil, *Citrus sinensis , Citrus sinensis (orange) peel oil, Citrus aurantium, Citrus aurantium dulcis (orange)* oil, *Citrus aurantium dulcis (orange) peel* oil is used in a wide range of cosmetic products in Canada (personal communication, emails from the Consumer Product Safety Directorate, 2015; unreferenced). In addition, sweet orange essential oil is present as a medicinal ingredient and Orange Oil Coldpressed, Orange Oil Distilled, and *Citrus aurantium dulcis (orange) peel* oil as non-medicinal ingredients in many natural health products (email from Natural and Non-Prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, July 2015; unreferenced).

Sweet orange oil is also listed as a fragrance ingredient used in consumer goods by the International Fragrance Association (IFRA 2017).

Information obtained pursuant to a section 71 survey under CEPA also reported uses as a solvent or odor agent in cleaning and furnishing care products, laundry and dishwashing products, as well as air care, apparel/footwear and automotive care products and lubricants/greases (Environment Canada 2013). Information from the American Cleaning Institute's (ACI) website indicates potential use of sweet orange oil as a fragrance in household cleaning products including all-purpose cleaners and dish and laundry care products (ACI 2017).

Sweet orange oil is used in alcoholic and non-alcoholic beverages, baked goods, candy/chewing gum, condiments, frozen dairy, gelatins/puddings, gravies and meat products (Burdock 2010). Sweet orange oil is listed in the US FDA Substances Added to Food inventory and in the Food Chemicals Codex as a flavouring agent (US FDA 2018; FCC 2018).

Additional uses for sweet orange oil are listed in Table 8.1-1.

Table 8.1-1. Additional uses in Canada for sweet orange oil

Use	Details
Food flavouring[a]	Reported uses in alcoholic and non-alcoholic beverages, baked goods, candy/chewing gum, condiments, frozen dairy, gelatins/puddings, gravies and meat products (Burdock 2010).
Natural Health Products Ingredients Database[b]	MI, NMI
Licensed Natural Health Products Database being present as a medicinal or non-medicinal ingredient in natural health products in Canada[b]	MI, NMI
Notified to be present in cosmetics, based on notifications submitted under the *Cosmetic Regulations* to Health Canada[c]	Skin, hair and oral care products, deodorants, fragrances and massage products.
Formulant in pest control products registered in Canada[d]	Formulant

Abbreviations: MI, medicinal ingredient; NMI, non-medicinal ingredient.

[a] Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced; Burdock 2010

[b] Email communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[c] Email communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[d] Email communication from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau; unreferenced

8.1.2 **Potential to cause harm to human health**

Sweet orange oil has been classified by the US Food and Drug Administration (US FDA) as generally recognized as safe (GRAS) when used as food flavouring agent or adjuvant (US FDA 2017a).

In considering environmental media, due to its high vapour pressure (192 Pa), limonene, the main component (84-96%) of sweet orange oil, is expected to partition almost completely to air (Kim et al. 2016).

Limonene has been measured in outdoor air in four Canadian studies in Windsor, Regina, Halifax, and Edmonton (HC 2010a, b, 2012, 2013). Concentrations of limonene in outdoor air from these Canadian studies ranged from less than the method detection limit to 111.60 µg/m^3 with geometric mean concentrations ranging from less than the method detection limit to 0.168 µg/m^3 across the studies.

Limonene was measured in the national Canadian indoor air study conducted in 2009-2011 as part of cycle 2 of the Canadian Health Measures Survey (CHMS). Limonene was detected in 99.84% of the samples with a geometric mean concentration of 21.30 µg/m^3 (weighted data at the household level) and a 95th percentile concentration of 228.1 µg/m^3 (Zhu et al. 2013). Limonene was also measured in indoor air in the four Canadian studies mentioned above. Concentrations of limonene in indoor air ranged from less than the method detection limit to 625.50 µg/m^3 with geometric mean concentrations ranging from 6.542 to 32.008 µg/m^3 across these Canadian indoor air monitoring studies. In addition, limonene has been detected in indoor air following new home construction (Won et al. 2017). Limonene has also been detected in a number of products available to consumers and building materials such as oil paint thinner and varnish, cleaning products, air fresheners, area rugs, laminated flooring, paint, adhesives, and I-beams (Won and Yang 2012; Won et al., 2013; Won et al., 2014).

Limited health effects information exists for sweet orange oil.

In a 28 day oral toxicity study, adverse effects were not observed after an administration of 0, 240, 600 and 1 500 mg/kg bw/day sweet orange oil in 1% methyl cellulose by gavage to male and female rats (US EPA 2018).

Sweet orange oil was also tested for toxicity in a reproductive and developmental toxicity screening test (US EPA 2018). Female rats were administered 0, 375, 750 or 1 500 mg/kg bw/day sweet orange oil via gavage for 28 days (7 days prior to co-habitation through to four days of lactation). At the highest dose level (1 500 mg/kg bw/day), only a significant increase in stillbirths and pup deaths was observed. Given that no adverse effects were observed approaching the limit dose for sweet orange oil, and further that no adverse effects were noted in developmental studies for the main component of sweet orange oil, no concerns for reproductive toxicity were identified.

Another study examined the safety and feasibility of the topical application of orange oil to the breast as an alternate means of drug delivery for limonene in breast cancer prevention or treatment (Miller et al. 2012). In the first part of this study, female SKH-1 mice (4 per group) were given either 10 or 20% orange oil in a base oil via gavage or applied topically. For the dermal studies, mice were fitted with collars for 20 minutes after application to prevent them from licking the oil. Adverse effects were not observed in both groups. In the second part of the study, the safety of applying orange oil dermally was evaluated in 44 women who massaged orange oil (3 drops in 1.35 mL base oil) into their breasts daily for 4 weeks. No other adverse effects were noted. Levels of limonene in the plasma and nipple aspirate fluid were not significantly different after the 4 week application, and levels in tissue were not measured.

Sweet orange oil was evaluated for genotoxicity in various test systems. In the bacterial reverse mutagenicity assay, sweet orange oil returned a negative result when tested with strains TA 1535, TA 1537, TA 1538, TA98 and TA100 with and without exogenous metabolic activation (Letizia et al. 2003). In the mamalian gene mutation assay with mouse lymphoma cells, sweet orange oil was positive both with and without metaboic activation (Letizia et al. 2003). However, the authors stated that the low pH associated with the test material may have confounded results and contributed to a positive outcome. In addition the positive results obtained with the addition of the metabolic activation occurred only at highly cytotoxic concentrations. Orange oil used as a food additive (identity of test material not provided) tested negative for chromosomal abberations in Chinese hamster fibroblast cells (Ishidate et al. 1983).

No studies regarding the chronic toxicity or carcinogenicity of sweet orange oil have been identified in the literature.

In order to further inform the risk assessment, the hazard information available for the main component of sweet orange oil, limonene (84-96%), has been considered.

Hazard assessment of main component

Limonene

Limonene is recognized as GRAS by the US FDA when used as flavouring agent or adjuvant (US FDA 2017a). Limonene has been reviewed previously by several international agencies including by the World Health Organization (WHO) in a 1998 Concise International Chemical Assessment Document (CICAD), by the Australian NICNAS in a 2002 priority existing chemical assessment, and by the US EPA in 2009 as a sponsored chemical (part of the Monoterpene Hydrocarbons category) under the HPV Challenge Program. These three assessments generally considered the same toxicity studies in their reviews. D-Limonene (CAS RN 5989-27-5), DL-Limonene (CAS RN 7705-14-8) and L-Limonene (CAS RN 5989-54-8) are recognized as GRAS by the US FDA when used as flavouring agents or adjuvants (US FDA 2018).

In terms of repeated dose studies, several studies showed effects in the kidney of rats and in the liver of rats and dogs. In one study, male rats were administered via gavage to 0, 2, 5, 10, 30, or 75 mg/kg bw/day of limonene five days per week for 13 weeks (Webb et al. 1989). The purpose of this study was to investigate the nephrotoxicity of limonene in male Fisher rats, which occurs via a mechanism not relevant to humans. Aside from the nephrotoxic effects, exposure to limonene was associated with increased liver weights at the two highest doses and a NOEL of 10 mg/kg bw/day was established. No concurrent histopathological changes were observed. In another study, exposure of rats to 400 mg/kg for 30 days resulted in 20-30% increase in liver enzymes, increased liver weight and decreased cholesterol levels (Ariyoshi et al. 1974). Exposure of dogs to 1.2 mL/kg bw/day (approx. 1000 mg/kg bw/day) limonene for 6 months resulted in increased liver enzymes and slightly increased liver weights (Webb et al. 1990).

In its risk characterization, the WHO's CICAD 1998 report uses the NOEL of 10 mg/kg bw/day based on increased liver weight in the rat as described in Webb et al. 1989. The CICAD report does note that no histopathological changes were observed in the liver and it further states that "The amount and activity of different liver enzymes were not investigated, and thus the increase in relative liver weight may be due to enzyme induction." In their review of limonene, NICNAS (2002) reports that although effects in the liver of rats and dogs were observed these effects are not related to toxicity but rather due to physiological adaptation. They conclude that for effects in the liver, it is not possible to identify a NOAEL. Given the lack of histopathological findings and the likelihood that effects in the liver are the result of physiological adaptation, the effects observed in the liver are not considered to be adverse.

In terms of developmental toxicity, the effects of limonene administered via gavage were evaluated in rats (0, 591, 2 869 mg/kg bw/day), mice (0, 591, 2 869 mg/kg bw/day), and rabbits (0, 250, 500, 1 000 mg/kg bw/day) (Webb et al. 1990, Tisserand and Young 2014). Limonene was not considered to be a developmental toxicant in any of the studies and effects in the offspring were only observed in the presence of maternal toxicity. In rats and mice, maternal toxicity was only observed at the 2869 mg/kg bw/day dose level. In rabbits, maternal deaths were observed at the highest dose group (1 000 mg/kg bw/day).

No concerns for genotoxicity were identified by any of the reviews. In terms of carcinogenicity, a two year study in male and female rats and mice was conducted by the NTP (1990). The study noted an increased incidence of hyperplasia and adenoma/adenocarcinoma in the kidney of male rats. However, this effect was not considered to be relevant for humans since the alpha-2μ-globulin protein linked to the effect is a male rat specific protein and is not present in humans. In 1999, IARC confirmed that there is sufficient evidence for carcinogenicity in animals, but insufficient evidence in humans, and thus concluded that limonene is not classifiable as to its carcinogenicity in humans (Group 3).

In terms of non-cancer effects in the NTP study, mice had an abnormal number of nuclei and cytomegaly in liver, but the response occurred only in male mice at the highest dose (500 mg/kg bw/day) (NTP 1990). Upon review of the data it was determined that this was likely a physiological adaptation. Adverse effects were not observed. This likelihood of the liver effects being a physical adaptation was confirmed in the NICNAS 2002 report. In addition, female rats had a significantly decreased survival rate at the highest dose tested (600 mg/kg bw/day) (NTP 1990). The European Food Safety Authority (EFSA) used a NOAEL of 215 mg/kg bw/day (300 mg/kg bw/day corrected for 5d/wk exposure) based on the decreased survival of female rats in the NTP study (EFSA 2015a).

The overall conclusion of these reviews was that, with the exception of its irritative and sensitizing properties (likely owing to oxidized limonene and not limonene itself), limonene can be considered a substance of fairly low toxicity. No other animal toxicity studies were identified in the literature subsequent to these reviews.

Volunteers were administered 10, 225, or 450 mg/m^3 of limonene in an exposure chamber on three different occasions for a two hour period each. The subjects did not experience any symptoms of irritation or any CNS related symptoms. A significant decrease in the vital capacity of volunteers was noted following exposure to the highest dose. However, this change was small in magnitude and deemed to be likely not functionally significant (Falk-Filipsson 1993).

Based on available information, health effects of concern were not identified. Accordingly, points of departure were not defined and a qualitative approach to risk characterization was taken. Exposure of the general population to sweet orange is, therefore, considered to be of low risk to human health.

8.2 Mandarin/tangerine oil

8.2.1 Sources and uses

Although mandarin and tangerine oils have different CAS RNs, their plant origin, *Citrus reticulata*, is identical and their names are used interchangeably in both health effect studies as well as listing of ingredients in products available to consumers and natural health products (unreferenced email communication from Consumer Product Safety Directorate and Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau and; Burdock 2010). As such, they will be assessed as one substance in this screening assessment report.

Mandarin and tangerine oils are naturally occurring substances that are derived from the cold expression of peel/rind of almost-ripe fruits or leaves of the *Citrus reticulata* plant species (Burdock 2010; Lota et al. 2000; Fleisher and Fleisher 1990). Based on information submitted pursuant to a section 71 survey under CEPA (Canada 2012), there were no reports of manufacture above the reporting threshold of 100 kg for mandarin or tangerine oils in 2011 (Environment Canada 2013). Between 100 and 1 000 kg of mandarin and tangerine oils was imported into Canada during the same calendar year (Environment Canada 2013).

Based on notifications submitted under the Cosmetic Regulations to Health Canada, mandarin/tangerine oils, *Citrus reticulata* peel oil (with various synonyms such as *C. nobilis*, *C. tangerina* and *C. depressa*), are used in greater than 675 cosmetic products in Canada in concentrations ranging from <0.1%-100%. Some of the product types reported include body lotion, massage products, cleansers, fragrance, make-up, hair care, and bath products. The majority of these products (>75%) contain mandarin/tangerine oil at a concentration range of 1% or less (personal communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau. Health Canada, 2016; unreferenced).

Information obtained pursuant to a section 71 survey under CEPA also reported mandarin oil uses in personal care products as an odor agent (Environment Canada 2013). It is also listed as a fragrance ingredient used in consumer goods by the

International Fragrance Association (IFRA 2017). The Skin Deep Cosmetics database website lists tangerine oil as a fragrance, skin conditioning and masking agent in cosmetics (EWG Skin Deep 2017). Tangerine oil is also listed as a fragrance ingredient used in consumer goods by the International Fragrance Association (IFRA 2017).

Information from the American Cleaning Institute's (ACI) website indicates potential use of mandarin oil as a fragrance in household cleaning products including all-purpose cleaners and dish and laundry care products (ACI 2017).

Both mandarin and tangerine oils are used in alcoholic and non-alcoholic beverages, baked goods, candy/chewing gum, frozen dairy and gelatins/puddings (Burdock 2010). Both oils are listed in the US FDA Substances Added to Food inventory and in the Food Chemicals Codex as a flavouring agent (US FDA 2018; FEMA 2017; FCC 2018). No definitive information is available concerning the potential use of mandarin or tangerine oil as food flavouring agents in Canada however since the substances are known to be used as a food flavouring agent in the US, it is possible that the substances are present as a flavouring agent in foods sold in Canada.

Additional uses for mandarin and tangerine oils are listed in Table 8.2-1.

Table 8.2-1. Additional uses in Canada for mandarin/tangerine oils

Use	Details
Food flavouring[a]	Reported uses in alcoholic and non-alcoholic beverages, baked goods, candy/chewing gum, frozen dairy, and gelatins/puddings (Burdock 2010).
Natural Health Products Ingredients Database[b]	NMI (flavor enhancer, fragrance ingredient or skin-conditioning agent in topical products)
Licensed Natural Health Products Database being present as a medicinal or non-medicinal ingredient in natural health products in Canada[b]	NMI
List of Prohibited and Restricted Cosmetic Ingredients[d]	Although mandarin and tangerine oil (CAS# 8008-31-9, 8016-85-1) are not present on the list of prohibited and restricted cosmetic ingredients, *Citrus reticulata* leaf oil (CAS# 8014-17-3) is identified as being prohibited on the Cosmetic Ingredient Hotlist at concentrations greater than 0.1% in leave-on products (HC 2015).
Notified to be present in cosmetics, based on notifications submitted under	Skin, hair and oral care products, deodorants, fragrances and massage products.

Use	Details
the *Cosmetic Regulations* to Health Canada[d]	
Formulant in pest control products registered in Canada[e]	Formulant

Abbreviations: NMI, non-medicinal ingredient.
[a] Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced; Burdock 2010
[b] Email communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced
[c] Email communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau; unreferenced
[d] Email communication from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau; unreferenced

8.2.2 Potential to cause harm to human health

8.2.2.1 Exposure assessment

In consideration of the low quantities of the substance reported to be used in Canada (Environment Canada 2013), an impact on human health from exposure to mandarin/tangerine oil from environmental media is not expected.

Dietary exposure of Canadians to both oils when used as food flavouring agents was estimated using the individual consumption of 1.12×10^{-2} mg/kg bw/day for mandarin oil and 5.52×10^{-2} mg/kg bw/day for tangerine oil leading to a combined dietary intake of 6.64×10^{-2} mg/kg bw/day for the US population established in Fenaroli's Handbook of Flavor Ingredients (personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2017; unreferenced).

To evaluate the potential for exposure to mandarin/tangerine oil from cosmetics, sentinel scenarios were selected based on a combination of use frequencies and reported concentrations of mandarin/tangerine oil in these products. These scenarios represented the highest exposure by the dermal route of administration, relative to other dermally applied cosmetics and natural health products based on identified products reported to contain the substance. Exposure to mandarin oil from the use of a body moisturizer, sunscreen, and massage oil were considered to be the sentinel scenarios by the dermal route of administration to estimate daily exposure. This data and full calculation is summarized in Appendix E (Tables E-1, E-2, and E-3).

The highest daily exposures by the dermal route of administration to mandarin/tangerine oil are expected to occur from the use of a body moisturizer, sunscreen, and massage oil with reported upper concentrations of 5%, 1%, and 100% (but with instructions to dilute a few drops into a carrier oil for the massage oil) mandarin/tangerine oil, respectively. Systemic exposure by the dermal and inhalation routes for body moisturizer and massage oil (assuming 20% dermal absorption for occluded skin for body moisturizer and 4% dermal absorption for unoccluded skin for massage oil) ranged

from 1.21-1.46 mg/kg bw/day and 1.12 x 10^{-1} – 1.33 x 10^{-1} mg/kg bw/day, respectively, for women of reproductive age. Systemic exposure by the dermal route from sunscreen (assuming 4% dermal absorption for unoccluded skin) ranged from 1.44 x 10^{-1} – 1.72 x 10^{-1} mg/kg bw/day mg/kg bw/day. In addition, systemic exposure by the dermal and inhalation routes for an adult mixing, loading, and applying an all-purpose cleaner (1% mandarin/tangerine oil) and mixing, loading, and hanging machine-washed laundry (5% mandarin/tangerine oil) was calculated to be 8.26 x 10^{-3} and 1.68 x 10^{-2} mg/kg bw/day, respectively. This data and all its parameters are summarized in Appendix E (Tables E-1 to E-3, and E-5 and E-6).

Many natural health products containing mandarin/tangerine oils as a non-medicinal ingredient are reported for topical use and therefore result in dermal exposure (e.g., acne treatment, lotions, and aromatherapy essential oils). Information on quantity of mandarin/tangerine oils was not available for most products (email from Natural and Non-Prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, July 2015; unreferenced); however, exposure to mandarin/tangerine oils from these natural health products is expected to be comparable or less than the highest estimates of dermal exposure to mandarin/tangerine oil from use of cosmetics or sunscreen.

Some natural health products were also reported for the oral route containing mandarin/tangerine oils as non-medicinal ingredients in vitamins, toothpaste, supplements, lozenges, and mouth wash. The highest systemic exposure by the oral route to mandarin/tangerine oil is expected from use of a dietary supplement with an estimated systemic exposure of 4.20 x 10^{-1} mg/kg bw/day.

Exposure by the inhalation route to mandarin/tangerine oils may result from the use of certain cosmetics (e.g., spray perfume) and aromatherapy. Mean concentration on the day of exposure from a perfume containing 30% mandarin/tangerine oil was determined to be 5.80 x 10^{-2} mg/m^3 (or systemic exposure ranging from 1.30 x 10^{-2} – 1.50 x 10^{-2} mg/kg bw/day for women of reproductive age) (full calculation parameters in Appendix-E, Table E-3). Inhalation exposure to mandarin/tangerine oil from an aromatherapy diffuser was calculated using a Danish EPA health assessment document of chemical substances in essential oils and fragrance oils (Danish EPA 2008). Details of the scenario and exposure parameters are outlined in Appendix D (Tables D1-D2). Systemic exposure by the inhalation route for aromatherapy ranged from 5.50 x 10^{-2} – 6.40 x 10^{-2} mg/kg bw/day for mandarin/tangerine oils.

8.2.2.2 Health effects assessment

Hazard assessment of mandarin and tangerine oils

Mandarin and tangerine oils have been classified by the US Food and Drug Administration (US FDA) as generally recognized as safe (GRAS) when used as food flavouring agent or adjuvant (US FDA 2017a).

No studies regarding the genotoxicity, carcinogenicity, sub-chronic, chronic or reproductive/developmental toxicity of mandarin or tangerine oil have been identified in the literature. Consequently, in order to inform the risk assessment, the hazard information available for the main components of tangerine and mandarin, limonene (52-96%) and gamma-terpinene (tr-61%), total citral (15-19%), methyl N-methylanthranilate (0-58%) and linalool (0.2-59%) have been considered to assess these subtances.

Hazard assessment of main components

Limonene

Limonene is considered a substance of fairly low toxicity. Further information on the health effects of limonene are provided in the Potential to cause harm to human health section for sweet orange oil (Section 8.1.2).

Gamma-Terpinene

Gamma-terpinene has been reported as being a component in mandarin (tr-61%) and tangerine oil (trace-4.5%). Alpha-terpinene and delta-terpinene are isomers and analogues of gamma-terpinene. The primary difference is the position of a double bond within the ring. All have comparable physicochemical properties and mechanistic profiles, test negative for Ames mutagenicity, and tend to form a few common metabolites (using rat liver S9 metabolic simulator) that have structural features associated with the potential to act as development or reproductive toxicants. This assessment was carried out using OECD QSAR Toolbox version 4.2, Oasis TIMES version 2.28, Leadscope Enterprise version 3.5 and the PubChem online database.

Pregnant female rats were administered 0, 30, 60, 125 or 250 mg/kg bw/day alpha-terpinene (89% pure) by gavage once daily from GD 6 to GD 15. A significant decrease of maternal weight gain has been observed at 250 mg/kg bw/day from the beginning of the exposure to the end of pregnancy. However, dams lost weight only during the treatment period (from GD5 to GD 15) at the 125 mg/kg bw/day dose group and it was reversible when the treatment stopped (from GD 15 to GD21). Although no consumption data is mentioned in the study, a decrease in food consumption during the treatment period due to the low palatability of the chemical may be responsible for the decrease in body weight. A significant decrease of fetal body weight was seen at 250 mg/kg bw/day. A significant increase of fetal anomalies in the skeleton such as shorter ribs and bifurcated basiphenoids, delayed ossification and organ weight was observed at 60 mg/kg bw/day and above. The study authors concluded that the results indicate that alpha-terpinene can adversely affect embryofetal development in the rat at oral doses of 60 mg/kg body weight or more and defined a NOAEL for embryofetotoxicity at 30 mg/kg bw/day. Although maternal body weight gain decreased at 250 mg/kg bw/day, in the absence of other signs of toxicity, this effect is not considered adverse (Araujo et al. 1996).

Adverse effects were not observed in a developmental study that fed male and female rats (10 animals/dose/sex except for control males and at top dose: 5 males/dose) with 0, 800, 2500 or 5000 ppm (corresponding to 0, 54, 155 or 301 mg/kg bw/day respectively) delta-terpinene for 42 days (mating, pregnancy and lactation) with a 14-day recovery period to (ECHA 2013). However, contrarily to Araujo et al. 1996, a skeleton analysis was not performed on offspring. Based on the results of this study, the NOAEL of delta-terpinene for reproductive toxicity, maternal and developmental effect was 5000 ppm (corresponding to 300.8 mg/kg bw/day).

Total Citral

Evaluation of citral by the Joint FAO/WHO Expert Committee on Food Additives has concluded that it does not present a safety concern as a food flavouring agent based on estimated levels of intake (WHO 2004b). Citral was not reported as a reproductive or a developmental toxicant (MHW, Japan 2002). A review of the literature of total citral found no concerns for genotoxicity or carcinogenicity. The critical effect level was a NOAEC of 215 mg/m^3 (34 ppm) (adjusted to 53.75 mg/m^3 to account for the 6hr/day exposure) as identified in a developmental toxicity study of citral in rats. The effect level was based on mortality and abortion in dams observed at 423 mg/m^3 (68 ppm) (Gaworski et al. 1992). Further information on the health effects of citral are provided in the Health effects assessment section for lemongrass oil (Section 7.7.2.2).

Methyl N-methyl anthranilate

Evaluation of methyl N-methyl anthranilate by the Joint FAO/WHO Expert Committee on Food Additives has concluded that it does not present a safety concern as a food flavouring (WHO 2006a). The Scientific Committee on consumer Safety (SCCS) of European Commission has concluded that methyl-N-methylanthranilate is phototoxic and a maximum of 0.1% methy-N-methylanthranilate may be safe for use in many leave-on cosmetic products, including deodorants and antiperspirants (SCCS 2011). However, the SCCS considers that for the use of products (including fragrances and sunscreen/sun care) intended for use on areas exposed to light (especially face and neck), a risk cannot be excluded (SCCS 2011).

Female and male rats were fed with 0, 300, 1 200 or 3 600 ppm (21, 82 or 244 mg/kg/bw for males and 24, 95 or 280 mg/kg bw for females) for 13 weeks. A statistically significant but very small (< 10%) increase was observed in absolute and relative kidney weights in animals at 1200 and 3600 mg/kg bw/day but no effect in histological examinations was observed (Gaunt and Sharratt 1970). Based on the absence of adverse effect in all doses, a NOAEL of 280 mg/kg/day was observed (WHO 2006a).

The European Chemical Agency (ECHA) predicted a NOAEL of 507 mg/kg bw/day for a dermal exposure and a NOAEL of 162.5 mg/m^3 for an inhalation exposure using QSAR Toolbox (Version 3.3) (ECHA 2015).

Linalool

A review of the literature of linalool found no concerns for genotoxicity or carcinogenicity. Moreover, no adverse effects were reported below 1 000 mg/kg bw/day in reproductive/developmental or short-term toxicity tests. Further information on the health effects of linalool are provided in the Potential to cause harm to human health section of this document for bois de rose oil (Section 7.1.2).

8.2.2.3 Characterization of risk to human health

The identified endpoint of concern was a developmental NOAEL of 30 mg/kg bw/day based on increased fetal abnormalities in the skeleton, delayed ossification and organ weight observed at 60 mg/kg bw/day from an oral developmental rat study conducted with alpha-terpinene (read-across to the main component gamma-terpinene). The vulnerable subpopulation is women of reproductive age (i.e. teens and adult women), and as such, risk has been characterized for this subpopulation only.

For dermal and inhalation routes of exposure, a route-to-route extrapolation was conducted using parameters listed in previous sections of the assessment.

For exposure by the inhalation route, the critical effect level established for citral, one of the components of mandarin/tangerine oil (15-19%) was also considered. The critical effect level was a NOAEC of 215 mg/m^3 (34 ppm) (adjusted to 53.75 mg/m^3 to account for the 6 hr/day exposure) based on mortality and abortion in dams observed at 423 mg/m^3 from a developmental toxicity study of citral in rats (Gawarski et al. 1992). As noted in lemongrass oil, as it was unknown whether the toxic effect observed was the result of a single exposure, and there was also severe respiratory tract irritation observed in the study, it was considered appropriate to compare air concentrations associated with the inhalation exposure scenario directly to the adjusted NOAEC from the inhalation study (Section 7.7.2). To ensure that any potential exposure to citral by the inhalation route from use of mandarin/tangerine oil would not present a concern, the highest air concentration of 1.45 mg/m^3 (24 hours) from the aromatherapy scenario adjusted by the upper concentration of citral present in mandarin and tangerine oil of 20% (0.29 mg/m^3) was compared to the adjusted NOAEC for citral of 53.75 mg/m^3. This resulted in a MOE of 185, which is considered adequate to account for any uncertainties in the database.

The main components of mandarin/tangerine oil are limonene (52-96%), gamma-terpinene (trace-61%), total citral (15-19%), methyl N-methylanthranilate (0-58%), and linalool (0.2-59%). In the absence of toxicological data for gamma-terpinene, alpha-terpinene was used as a read-across analogue for gamma-terpinene to inform the risk characterization of mandarin/tangerine oil. As there were no toxicological effects of concern identified for the other main components of mandarin/tangerine oil besides the critical effect level by the inhalation route for citral identified above, and phototoxicity

associated with methyl N-methylanthranilate, it was considered appropriate to adjust all exposure estimates by 60%, which represents the maximum amount of gamma-terpinene in mandarin/tangerine oil (Lota et al. 2000). This is a conservative approach as it assumes that the amount of gamma-terpinene in mandarin/tangerine oil is equivalent to the maximum amount that has been detected, and it also assumes that the toxicity of gamma and alpha-terpinene is equivalent.

Table 8.2-2. Relevant exposure estimates, critical effect levels and resulting margins of exposure for gamma-terpinene in mandarin/tangerine oil

Exposure Scenario[a]	**Systemic Exposure (mg/kg bw/day)[b]**	**MOE[c]**
Food flavoring (dietary intake)	3.98×10^{-2} (6 months and above)	754 (6 months and above)
Systemic exposure by the dermal and inhalation routes from body lotion (5%)[d]	$7.25 \times 10^{-1} – 8.74 \times 10^{-1}$ (teen-adult)	**34 - 41** (adult-teen)
Systemic exposure by the dermal route from sunscreen (1%)[e,g]	8.63×10^{-2} - 1.03×10^{-1} (adult-teen)	291 - 348 (teen–adult)
Systemic exposure by the inhalation route from fragrance product (30%) (5.8×10^{-2} mg/m^3)	8.00×10^{-3}- 9.00×10^{-3} (adult-teen)	3750 - 3333 (teen–adult)
Systemic exposure by the dermal and inhalation routes from massage oil (4 drops from 100% upper concentration)[e]	$6.71 \times 10^{-2} – 8.00 \times 10^{-2}$ (adult-teen)	375 - 447 (teen-adult)
Systemic exposure by the inhalation route from aromatherapy (1.45 mg/m^3)[f]	$3.00 \times 10^{-2} – 4.00 \times 10^{-2}$ (adult-teen)	750 - 1 000 (teen-adult)
Systemic exposure by the dermal and inhalation routes from mixing, loading, and application of a liquid all-purpose cleaner (1%)[e]	4.95×10^{-3} (adult)	6 060 (adult)
Systemic exposure by the dermal and inhalation routes from mixing, loading and hanging machine-washed laundry (5%)[e]	1.01×10^{-2} (adult)	2 969 (adult)
Non-medicinal ingredient in dietary supplements	2.54×10^{-1} (adult)	**118** (adult)

[a] Exposure scenario parameters and calculations for mandarin/tangerine oils outlined in Appendix E
[b] Adjusted by 60% for the maximum amount of gamma-terpinene in mandarin/tangerine oils (61% in leaf, Lota et al. 2000)
[c] Margin of exposure calculated using the critical effect level (NOAEL = 30 mg/kg bw/day) for gamma-terpinene based on increased fetal abnormalities in the skeleton, delayed ossification and organ weight from an oral developmental rat study conducted with alpha-terpinene (read-across to gamma-terpinene).
[d] Assuming dermal absorption of 20% (occluded)
[e] Assuming dermal absorption of 4% (unoccluded)
[f] Refer to Appendix D for Aromatherapy Scenario details

[g] Inhalation exposure for sunscreen scenarios was not quantified, as it was assumed that sunscreen products would be used outdoors and any exposure by the inhalation route would be minimal in comparison to the dermal route.

The margin of exposure between the critical effect level and the estimate of daily exposure to mandarin oil from a body moisturizer ranged from 34 - 41. In addition, the calculated margin of exposure for a dietary supplement was 118. These margins of exposures are considered potentially inadequate to account for uncertainties in the health effects and exposure databases.

For all other scenarios, the margins of exposure between the critical effect level and the estimate of exposure are considered to be adequate to account for uncertainties in the health effects and exposure databases.

8.2.2.4 Uncertainties in evaluation of risk to human health

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

Table 8.2-3. Sources of uncertainty in the risk characterization for mandarin/tangerine oils

Key source of uncertainty	Impact
Exposure	
Exposure estimates from the use of mandarin/tangerine oil in sunscreen did not consider potential exposure to mandarin/tangerine oil from the inhalation route; which may underestimate total systemic exposure due to the volatility of mandarin/tangerine oil. However, as sunscreen is generally used outdoors, the contribution of the inhalation route to overall systemic exposure is not expected to be significant.	-
Combining both the dermal and inhalation routes for the cleaning scenarios, and the use of conservative assumptions to calculate exposure from each route of exposure, may result in conservative estimates.	+
Inhalation estimates for mandarin/tangerine oil in products is very dependent upon factors such as room volume, ventilation rates, time spent in area of application and calculation of the time-weighted average. Each of these parameters has variability and uncertainty. Conservative assumptions were used.	+
There is a degree of uncertainty in extrapolating the dermal absorption data from linalool and citronellol to mandarin/tangerine oil; however, as all the acyclic/monocyclic/bicyclic monoterpenes and constituents thereof have similar physical-chemical properties, the dermal absorption of these compounds is expected to be similar.	+/-
Route-to-route extrapolation for mandarin/tangerine oil was carried out for dermal and inhalation scenarios in comparing to an effect level from an oral study.	+/-
Hazard	

Key source of uncertainty	Impact
There are no studies for dermal or inhalation exposure.	+/-
The critical effect study for alpha-terpinene had a purity of 89%. This represents an uncertainty as it is unknown whether the critical effects observed could have been a result of another substance.	+/-
Using the main component of mandarin/tangerine oil to inform the health effects assessment (i.e. gamma-terpinene). Due to the wide variability in concentrations of gamma-terpinene (trace-61%) in mandarin/tangerine oil, the potential hazard associated with gamma-terpinene may not be reflective of mandarin/tangerine oil.	+
Using read-across to alpha-terpinene and delta-terpinene for gamma-terpinene. This is considered a conservative approach as it was assumed that the hazard observed with alpha-terpinene is reflective of mandarin/tangerine oil.	+

+ = 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.

8.3 Alpha-pinene

8.3.1 Sources and uses

Alpha-pinene is a naturally occurring substance obtained by distillation of turpentine. It has been reported in over 400 different essential oils, with the highest levels found in *Achillea millefolium*, *Artemisia tridentata*, Italian rosemary, wild thyme, French lavender, coriander and cumin (Burdock 2010). It is also reported in over 200 natural products including many fruits, vegetables, spices and herbs (Burdock 2010).

Based on information submitted pursuant to a section 71 survey under CEPA (Canada 2009), between 1 000 000 and 10 000 000 kg of alpha-pinene was manufactured in Canada in 2008 and between 500 and 5300 kg was imported in the same calendar year (Environment Canada 2009).

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, alpha-pinene is present in a limited number of cosmetic products at concentrations ranging from <0.1%-30% (personal communication, emails from the Consumer Product Safety Directorate (CPSD), 2017; unreferenced). Some of the product types reported include a face mist, cleansers, fragrance products, conditioners, and bath products. The majority of products (>60%) contain alpha pinene at a concentration range of 1% or less.

It is also listed as a fragrance ingredient used in consumer goods by the International Fragrance Association (IFRA 2017).

Information obtained pursuant to a section 71 survey under CEPA also reported uses in food packaging, paper products, paints/coatings, building/construction wood materials

as being incidentally produced during the pulping process (Environment Canada 2009). Alpha-pinene is also found in car air fresheners (MSDS 2004).

Alpha-pinene is used in alcoholic and non-alcoholic beverages, baked goods, candy/chewing gum, condiments, frozen dairy, gelatins/puddings and meat products (Burdock 2010). Alpha-pinene is listed in the US FDA Substances Added to Food inventory, in the Food Chemicals Codex, and in the EU Food Flavourings Database as a flavouring agent (US FDA 2018; WHO 2006b; FEMA 2017; FCC 2018; EU 2016). No definitive information is available concerning the potential use of alpha-pinene as a food flavouring agent in Canada however since the substance is known to be used as a food flavouring agent in the US, it is possible that it is present as a flavouring agent in foods sold in Canada.

Additional uses for alpha-pinene are listed in Table 8.3-1.

Table 8.3-1. Additional uses in Canada for alpha-pinene

Use	Details
Food flavouring[a]	Reported uses in alcoholic and non-alcoholic beverages, baked goods, candy/chewing gum, condiments, frozen dairy, gelatins/puddings and meat products (Burdock 2010).
Natural Health Products Ingredients Database[b]	NMI
Licensed Natural Health Products Database being present as a medicinal or non-medicinal ingredient in natural health products in Canada[b]	NMI
Notified to be present in cosmetics, based on notifications submitted under the *Cosmetic Regulations* to Health Canada[c]	Skin and hair care products (lotions/cleansers), and fragrances.
Formulant in pest control products registered in Canada[d]	Formulant

Abbreviations: NMI, non-medicinal ingredient.

[a] Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced; Burdock 2010

[b] Email communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[c] Email communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[d] Email communication from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau; unreferenced

8.3.2 Potential to cause harm to human health

8.3.2.1 Exposure assessment

In considering environmental media, due to its high vapour pressure (633 Pa), alpha-pinene is expected to partition almost completely to air (Kim et al. 2016). In addition, due to its low water solubility (2.49 mg/L) and its very high Henry's law constant (0.30 [atm-m^3/mol]), alpha-pinene is expected to volatilize rapidly from water surfaces.

As alpha-pinene is a naturally occurring substance in coniferous trees, a major source of alpha-pinene in outdoor and indoor air, is its emittance from trees and its release from wood products, respectively (NTP 2002).

Outdoor air

Alpha-pinene has been reported to Environment and Climate Change Canada's National Pollutant Release Inventory (NPRI), where 4,751,000 kg (4751 tonnes) were released on-site to air from various Canadian companies during the 2015 reporting year (ECCC 2016c). When examining reported releases of alpha-pinene with respect to proximity to residential areas, a sentinel engineered wood product manufacturing facility was identified where releases of 83,300 kg (83.3 tonnes) were within 200-500 m of a residential area (ECCC 2016c); therefore, concentrations at 200 m from the emission source were chosen to simulate potential exposure from industrial release of alpha-pinene. SCREEN3, a tier-one screening-level Gaussian air dispersion model, was used to model the contribution of alpha-pinene to ambient air associated with these industrial releases (SCREEN3 1996). The SCREEN3 model was developed based on the Industrial Source Complex (ISC) model (for assessing pollutant concentrations from various sources in an industry complex). SCREEN3 is designed to estimate maximum concentrations of chemicals at chosen receptor heights and at various distances from a release source for a given continuous emission event. 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. The driver for air dispersion in the SCREEN3 model is wind. This model directly predicts concentrations resulting from point, area and volume source releases. SCREEN3 provides the maximum exposure concentration in the direction downwind from the prevalent wind 1 hour after the release event. With an assumption of a continuous release occurring over a 24-hour period and considering the changing wind direction over this period, a maximum concentration during a 24-hour exposure period is estimated by multiplying by a factor of 0.4. For exposures over the span of a year, it can be expected that with changing wind directions the substance air concentrations within an area release source may not vary to the same extent as those of point release sources; the meteorological conditions giving rise to a maximum 1-hour exposure can persist for a longer duration; thus, the maximum concentration for one year is determined by multiplying the maximum 1-hour concentration by a factor of 0.2. The results are adopted herein and are provided in Appendix F (Tables F-4 and F-5). As

presented in Table F-5, the annual upper-bounding estimate of alpha-pinene releases at 200 m was 6.76 µg/m^3 (point source release).

Alpha pinene has been measured in outdoor air in four Canadian studies in Windsor, Regina, Halifax, and Edmonton (HC 2010a, b, 2012, 2013). Concentrations of alpha pinene in outdoor air from these Canadian studies ranged from less than the method detection limit to 8.33 µg/m^3 with geometric mean concentrations ranging from less than the method detection limit to 0.32 µg/m^3 across the studies. The highest 95th percentile concentration of alpha pinene in outdoor air based on a large sample size (i.e., >30) was selected as being representative of general population for outdoor air exposure (1.55 µg/m^3 based on 24 hour samples from the Regina study) (HC 2010b).

Indoor air

Alpha-pinene was measured in the national Canadian indoor air study conducted in 2009-2011 as part of cycle 2 of the Canadian Health Measures Survey (CHMS). Alpha-pinene was detected in 99.92% of the samples with a geometric mean concentration of 5.62 µg/m^3 (weighted data at the household level) and a 95th percentile concentration of 43.45 µg/m^3 (Zhu et al. 2013).

Alpha pinene was also measured in indoor air in the four Canadian studies mentioned above. Concentrations of alpha pinene in indoor air ranged from less than the method detection limit to 1 010 µg/m^3 with geometric mean concentrations ranging from 0.30 to 26.86 µg/m^3 across these Canadian indoor air monitoring studies. The highest 95th percentile indoor air concentration measurement from the four studies was 380.63 µg/m^3 based on data from the Windsor study (HC 2010a).

Personal air sampling was also carried out in the Windsor exposure assessment study where adult participants carried a 1.0 L VOC canister, deployed every 24 hours for five consecutive days. Concentrations of alpha pinene in personal air samples ranged from 0.66 to 1 199.74 µg/m^3. The geometric means of the personal sampling measurements taken in winter and summer were 7.37 µg/m^3 and 33.09 µg/m^3, respectively, whereas the 95th percentiles for winter and summer measurements were 59.29 µg/m^3 and 531.80 µg/m^3, respectively (HC 2010a).

In addition, alpha-pinene has been measured in indoor air following new home construction with the major contributor being hardwood floors (Won et al. 2017). Alpha-pinene has also been reported to be emitted from building material samples in Canada including caulking, ceiling tiles, carpet, counter top, gypsum wallboard, laminate flooring, medium density fiberboard, oriented strand board, solid pine, plywood, I-beam joists and gypsum panel. The highest emissions of alpha-pinene at 24 hours were from solid pine (968.5 µg/m^3), I-beam joists (22.0 – 363.0 µg/m^3), plywood (125.7 µg/m^3), and gypsum wallboard (42.1 µg/m^3) (Won et al. 2013, 2014, Won and Lusztyk 2011). Chamber air concentrations at 24 hours ranged from 0.01 to 968.5 µg/m^3 (Won and Lusztyk 2011). Furthermore, emissions of alpha-pinene have been observed from flooring underpad, flooring composite, furniture, paint thinner and varnish, and air

fresheners (Won and Yang 2012). These sources are considered to be addressed as part of the assessment of indoor air exposure.

Food and products available to consumers

The per capita intake (PCI) of alpha pinene oil from its use as a food flavouring agent was estimated to be 2.44 mg/person per day for the US population based on JECFA's (Joint FAO/WHO Expert Committee on Food Additives) safety evaluation of food flavouring agents at its 63rd meeting (WHO 2006b) (personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2018; unreferenced). This in turn yields an estimated intake of 3.40×10^{-2} mg/kg bw/day (based on 70.9 kg adult body weight).

The Committee also determined the relative consumption of alpha-pinene from its natural occurrence in foods to be approximately 10-fold higher than consumption from its use as a flavouring based on the estimated annual consumption of various foods in the United States and data on the quantitative occurrence of α-pinene in foods (Stofberg and Grundschober 1987). Accordingly, the dietary exposure to α-pinene from its natural occurrence in foods is estimated to be 24.4 mg/ person per day for the US population (approximately 4.10×10^{-1} mg/kg bw per day).

To evaluate the potential for exposure to alpha-pinene by the dermal route of administration from cosmetics, a sentinel scenario was selected based on a combination of use frequencies and reported concentrations of alpha-pinene in the product. The highest daily exposure to alpha-pinene is expected to occur from the use of liquid oil as a face mist with a reported upper concentration of 10%. Systemic exposure by the dermal and inhalation routes for the face mist (assuming 4% dermal absorption) ranged from 3.66×10^{-1} – 4.28×10^{-1} mg/kg bw/day (adult-adolescent). In addition, systemic exposure by the dermal, inhalation and non-dietary ingestion routes to a toddler coming into contact with cleaned floor (containing 1% alpha-pinene) was calculated to be 4.22×10^{-2} mg/kg bw/day while systemic exposure by the dermal and inhalation routes for an adult mixing, loading, and applying an all-purpose cleaner (also containing 1% alpha-pinene) was calculated to be 1.75×10^{-2} mg/kg bw/day. This data and all its parameters are summarized in Appendix F, Tables F-1 to F-3).

Exposure by the inhalation route to alpha-pinene may result from an aromatherapy diffuser which was calculated using a Danish EPA health assessment document of chemical substances in essential oils and fragrance oils (Danish EPA 2008). Details of the scenario and exposure parameters are outlined in Appendix D (Tables D1 and D3). Exposure by the inhalation route may also result from the use of a gel air freshener (containing 1-5% alpha-pinene). Systemic exposure by the inhalation route ranged from 5.53×10^{-2} – 1.45×10^{-1} mg/kg bw/day (adult-toddler) and 8.00×10^{-3} – 2.10×10^{-2} mg/kg bw/day) (adult-toddler) for aromatherapy and gel air freshener, respectively.

8.3.2.2 Health effects assessment

Alpha-pinene was evaluated internationally by the Joint FAO/WHO Expert Committee on Food Additives and was not considered to present a safety concern as a food flavouring agent based on estimated levels of intake (WHO 2006b). The US FDA indicates that alpha-pinene may be safely used as a flavouring agent in food when used in the minimum quantity required to produce the intended effect (US FDA 2017b).

Limited toxicological data is available for alpha-pinene.

Alpha-pinene underwent a screening-level hazard characterization by the US EPA in 2010 as a sponsored chemical (part of the Bicyclic Terpene Hydrocarbons category) under the HPV Challenge Program (US EPA 2010). The US EPA used read-across values from camphene (another substance evaluated in the same bicyclic terpene hydrocarbon category) in order to define an oral NOAEL of 250 mg/kg bw/day and a LOAEL of 1 000 mg/kg bw/day (US EPA 2010).

Two groups of rats and mice (5/sex/dose) were exposed via inhalation of the whole body to 100 to 1 600 ppm (557-8 912 mg/m^3) vapor of alpha-pinene for 6 hrs per day plus 10 minutes, 5 days per week for a dose-ranging 2-week study (NTP 2016). All rats and mice exposed to 800 and 1,600 ppm died within the first week. At 400 ppm, male and female rats showed an increase in relative liver and kidney weights. An increase of relative liver and kidney weights was also observed in male mice, but not in females for kidney. An increase in absolute and relative kidney weight only in females exposed to 100 ppm was observed. No histopathologic analyses were performed. A NOAEC of 200 ppm (1 246 mg/kg bw/day or NOAELadj = 222 mg/kg bw/day) and a LOAEC of 400 ppm (2 492 mg/kg bw/day or NOAELadj = 445 mg/kg bw/day) were determined for short-term exposure based on significantly decreased body weight of female rats and mice, and increased relative liver and kidney weights in rats and mice at 400 ppm by study authors (NTP 2016).

Two groups of rats and mice (10/sex/dose) were administered via inhalation to the whole body to 25 to 400 ppm (139-2 228 mg/m^3) vapor of alpha-pinene for 6 hrs per day plus 10 minutes, 5 days per week for 14-weeks (NTP 2016). Female rat appeared to be more sensitive than male as six out of ten female rats administered the highest dose died before the end of the study (NTP 2016). Both male and female rats had increased liver weights at 400 ppm. Female rats had increased kidney weights at 50 and 200 ppm. Male rats had decreased sperm per cauda at 200 and 400 ppm. Male and female mice had increased incidences of transitional epithelium hyperplasia of the urinary bladder at 100 ppm and above, as well as increased liver weights at 400 ppm. Male mice also had decreased sperm per cauda at 100 ppm and above. A NOAEC of 50 ppm (66 mg/kg bw/day) and LOAEC of 100 ppm (122 mg/kg bw/day) were determined for long-term exposure based on significantly increased incidences of transitional epithelium hyperplasia in the bladder of male and female mice at and above 100 ppm, and decreased sperm cauda in male mice at and above 100 ppm by study authours (NTP 2016).

Alpha-pinene was negative in Ames assay and the in vivo micronucleus assay. In contrast, in another study, exposure to alpha-pinene in vitro showed an increase in the aneugenic (chromosomal aberration) and clastogenic effects (micronuclei) in Chinese hamster V-79 cells. These effects were accompanied by increased reactive oxygen species production and mitotic alterations (Catanzaro et al. 2012).

In human volunteers, the uptake, distribution, and elimination of alpha-pinene was investigated following a short single inhalation exposure of 2 hour to 0, 10, 225, or 450 mg/m3 alpha-pinene in an exposure chamber (Falk et al. 1990). The uptake of alpha-pinene was high and the clearance from the blood was rapid indicating that it is readily metabolized. The elimination of alpha-pinene was considered to be triphasic with the appearance occurring rapidly after 4.8 and 5.6 minutes, a rapid elimination phase after 38 and 40 minutes and a slower elimination phase after 695 and 555 minutes for (+)- and (-) alpha-pinene respectively. Although clearance from the blood was initially rapid, the longer half-life indicates a high affinity of alpha-pinene for poorly perfused tissues such as adipose tissues. The study also showed that there was a significant dose related increase in symptoms of irritation of the eyes, nose and throat of the five subjects. The short-term exposure did not, however, result in effects on the central nervous system or changes to lung function.

8.3.2.3 Characterization of risk to human health

The critical effect level identified for alpha-pinene is a NOAEC of 50 ppm (equivalent to 66 mg/kg bw/day or 49.73 mg/m^3 when corrected for an exposure of 6 hours per day and 5 days per week, see Appendix F-6 for dose conversions) as identified in the 14-week NTP study (NTP 2016). The effect level is based on significantly increased incidences of transitional epithelium hyperplasia in the bladder of male and female mice at and above 100 ppm (equivalent to 118 mg/kg bw/day when corrected for an exposure of 6 hours per day and 5 days per week) and decreased sperm cauda in male mice at and above 100 ppm.

No health effects data were identified for alpha-pinene by the oral or dermal route of exposure. Consequently, route- to-route extrapolation from inhalation to oral was performed. The inhalation NOAEC of 50 ppm was converted to an oral dose (equivalent to 66 mg/kg bw/day when corrected for an exposure of 6 hours per day and 5 days per week) using standard values for inhalation and body weights. It was assumed that absorption via inhalation and oral routes were equivalent. The US EPA recommended an oral NOAEL of 250 mg/kg bw/day for alpha-pinene based on read-across from camphene. However, in the present assessment the data for alpha-pinene was considered to be more relevant and conservative.

As all of the exposure scenarios for alpha-pinene are considered to be chronic in duration (i.e. products used on a daily or weekly basis), the results from the 2 week range-finding study were not used in the risk characterization of alpha-pinene.

The critical effects from the 14-week inhalation study were systemic in nature (i.e. transitional epithelium hyperplasia in the bladder and decreased sperm cauda), and are expected to occur following repeated exposures since they were not observed in the 2-week range-finding study. Therefore, it was considered appropriate to calculate inhalation exposures on a per kg basis and compare the inhalation exposure to an adjusted systemic dose from the inhalation study. Systemic inhalation exposures were calculated using the 24-hour time weighted average air concentration from the exposure scenario and standard daily inhalation rates and body weights as outlined in Health Canada, 1998.

Table 8.3-2. Relevant exposure estimates, critical effect levels and resulting margins of exposure, for alpha-pinene

Exposure Scenario[a]	**Systemic Exposure (mg/kg bw/day)**	**MOE[b]**
Systemic exposure by the inhalation and dietary route from environmental media (air + food favoring + food natural occurrence)	$3.20 \times 10^{-1} – 5.73 \times 10^{-1}$ (95^{th} percentile) (toddler-adult) $2.00 \times 10^{-2} – 4.59 \times 10^{-1}$ (geometric mean) (toddler–adult)	115 - 206 (95^{th} percentile) (adult–toddler) 144 - 3 293 (geometric mean) (adult–toddler)
Systemic exposure by the inhalation route from environmental media (indoor air)	$1.22 \times 10^{-1} – 3.19 \times 10^{-1}$ (adult-toddler)	207 - 543 (toddler-adult)
Systemic exposure by inhalation route from industrial release (outdoor air)	$1.54 \times 10^{-3} – 4.06 \times 10^{-3}$ (adult-toddler)	16 272 - 42 730 (toddler–adult)
Systemic exposure by the dermal and inhalation route from face mist (10%)[c] (adolescent-adult)	$3.66 \times 10^{-1} – 4.28 \times 10^{-1}$ (adult-adolescent)	154 - 180 (adolescent–adult)
Systemic exposure by the dermal and inhalation route from mixing, loading, and application of an all-purpose cleaner (1%)[c]	1.75×10^{-2} (adult)	3 771 (adult)
Systemic exposure by dermal, inhalation, and non-dietary ingestion route from contacting cleaned floors (1%)[c]	4.23×10^{-2} (toddler)	1 561 (toddler)
Systemic exposure by the dermal and inhalation route from mixing, loading, washing and hanging hand-washed laundry (1%)[c]	1.73×10^{-2} (adult)	3 815 (adult)
Systemic exposure by the inhalation route from aromatherapy [d]	$5.53 \times 10^{-2} – 1.45 \times 10^{-1}$ (adult-toddler)	455 - 1 194 (toddler–adult)

Exposure Scenario[a]	Systemic Exposure (mg/kg bw/day)	MOE[b]
Systemic exposure by the inhalation route from gel air freshener (5%)	8.00×10^{-3} – 2.10×10^{-2} (adult-toddler)	3 143 - 8 253 (toddler–adult)

[a] Exposure scenario parameters and calculations for alpha-pinene outlined in Appendix F
[b] Margin of exposure was calculated using the critical effect level ($NOAEL_{adj}$ = 66 mg/kg bw/day) based on transitional epithelium hyperplasia in the bladder (male and female) and decreased sperm cauda (male) from a 14-week inhalation study of alpha-pinene in mice.
[c] Assuming dermal absorption of 4% (unoccluded)
[d] Refer to Appendix D for Aromatherapy Scenario details

For all scenarios, the margin of exposure between the critical effect level and the estimate of exposure for scenarios listed in Table 8-3-2 are considered adequate to account for uncertainties in the health effects and exposure databases.

8.3.2.4 Uncertainties in evaluation of risk to human health

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

Table 8.3-3. Sources of uncertainty in the risk characterization for alpha-pinene

Key source of Uncertainty	Impact
Exposure	
Combining both the dermal and inhalation routes for the cleaning scenarios, and the use of conservative assumptions to calculate exposure from each route of exposure, may result in conservative estimates.	+
Inhalation estimates for alpha-pinene in products is very dependent upon factors such as room volume, ventilation rates, time spent in area of application and calculation of the time-weighted average. Each of these parameters has variability and uncertainty. Conservative assumptions were used.	+
There is a degree of uncertainty in extrapolating the dermal absorption data from linalool and citronellol to alpha-pinene; however, as all the acyclic/monocyclic/bicyclic monoterpenes and constituents thereof have similar physical-chemical properties, the dermal absorption of these compounds is expected to be similar.	+/-
Route-to-route extrapolation for alpha-pinene was carried out for dermal scenarios in comparing to an effect level from an inhalation study.	+/-
Hazard	
There is limited information on repeated-dose effects via relevant routes of exposure and different durations for alpha-pinene.	+/-

+ = 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.

8.4 Turpentine oil/Turpentine

8.4.1 Sources and uses

Turpentine is a naturally occurring substance obtained from the semi-fluid oleoresins of coniferous trees from various *Pinus spp*., primarily *Pinus palustris* (NTP 2002; Burdock 2010). Turpentine (CASRN 9005-90-7) and turpentine oil (CASRN 8006-64-2) are often used interchangeably and the definitions in the literature are inconsistent; however, their compositions are practically identical.

The main components of turpentine/turpentine oil have been reported in the literature as alpha-pinene (44-94%), beta-pinene (0.9-30%), limonene (0.7-25%), and camphene (1-15%) (Tisserand and Young 2014; NTP 2002). However, a recent preliminary analysis of turpentine oils available at Canadian hardware stores indicated that the main components of the volatile fraction are limonene, terpinolene, and approximately 20% alpha and gamma terpinene. The same compositional analysis confirmed that the main components of the volatile fraction of turpentine/turpentine oils available at art supply stores were alpha-pinene and beta-pinene (HC 2019).

Based on information submitted pursuant to a section 71 survey under CEPA (Canada 2012), approximately 18 000 000 kg of turpentine was manufactured in Canada in 2011 (Environment Canada 2013). There were no reports of import above the reporting threshold of 100 kg for turpentine in the same calendar year (Environment Canada 2013).

CASRN 8006-64-2 was not surveyed under section 71 of CEPA. However, in the US, annual production and/or import volume was between 100 000 000 and 500 000 000 lbs in the calendar year 2005 (US EPA 2010).

According to the Canadian International Merchandise Trade Database (CIMT), ‘gum, wood or sulphate turpentine oils’ HS Code (380510) was imported at an approximate average of 17 000 kg to Canada from the years 2014-2017 (CIMT 2017).

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, turpentine/turpentine oil is present in a limited number of cosmetic products in Canada at concentrations of 0.1% or less reported (personal communication, emails from the Consumer Product Safety Directorate, 2017; unreferenced).

Information obtained pursuant to a section 71 survey under CEPA reported uses as an odor agent in cleaning and furnishing care products, laundry and dishwashing products, air care, apparel and footwear care as well as automotive products and lubricants/greases (Environment Canada 2013).

Turpentine is also listed as a fragrance ingredient used in consumer goods by the International Fragrance Association (IFRA 2017).

Turpentine oil is also found in automotive care products (SDS 2013) and turpentine solvents (MSDS 2013).

Turpentine is used in baked goods (Burdock 2010) and listed in the US FDA Substances Added to Food inventory and in the Food Chemicals Codex as a flavouring agent (US FDA 2018). Turpentine oil is used in alcoholic and non-alcoholic beverages, baked goods, candy/chewing gum, condiments, frozen dairy, gelatins/puddings and meat products (Burdock 2010). Turpentine oil is listed in the US FDA Substances Added to Food inventory and in the Food Chemicals Codex as a flavouring agent (US FDA 2018). No definitive information is available concerning the potential use of turpentine and turpentine oil as food flavouring agent in Canada however since the substances are known to be used as food flavouring agents in the US, it is possible that they are present as flavouring agents in foods sold in Canada.

Previously, turpentine was used as the most popular paint and varnish thinner, however presently it has been replaced by less expensive petroleum-based products in paints. Currently, it is mostly in “specialty applications such as spray painting, pottery and ceramic coatings, artist’s paints, and naval paints”. It can also be present in shoe and furniture polishes (NTP 2002).

Additional uses for turpentine oil are listed in Table 8.4-1.

Table 8.4-1. Additional uses in Canada for turpentine/turpentine oil

Use	Turpentine oil (CASRN 8006-64-2)	Turpentine (CASRN 9005-90-7)
Food flavouring[a]	Y	Y
Incidental additives[a]	Component in cleaners, no potential for direct food contact because use is followed by a potable water rinse.	N
Natural Health Products Ingredients Database[b]	Y- MI, NMI (base, fragrance ingredient, viscosity decreasing agent)	N
Licensed Natural Health Products Database being present as a medicinal or non-medicinal ingredient in natural health products in Canada[b]	Y- MI, NMI	Y - NMI
Notified to be present in cosmetics, based on notifications submitted under the *Cosmetic*	Y (skin, hair care and massage products)	Y (skin, hair care and massage products)

Use	Turpentine oil (CASRN 8006-64-2)	Turpentine (CASRN 9005-90-7)
Regulations to Health Canada[c]		
Formulant in pest control products registered in Canada[d]	Y	Y

Abbreviations: Y, use was reported for this substance; N, use was not reported for this substance; MI, medicinal ingredient; NMI, non-medicinal ingredient.

[a] Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[b] Email communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[c] Email communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[d] Email communication from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau; unreferenced

8.4.2 Potential to cause harm to human health

8.4.2.1 Exposure assessment

In considering environmental media, alpha-pinene (which makes up 44-94% of turpentine/turpentine oil) was used to inform the partitioning to the environment. Due to its high vapour pressure (633 Pa), alpha-pinene is expected to partition almost completely to air (Kim et al. 2016). In addition, due to its low water solubility (2.49 mg/L) and its very high Henry's law constant (0.30 [atm-m^3/mol]), alpha-pinene is expected to volatilize rapidly from water surfaces.

No air monitoring data was found for turpentine oil; however its major constituent alpha-pinene is addressed in Section 8.3.2.1.

Dietary exposure of Canadians to turpentine and turpentine oil when used as a food flavouring agent was estimated based on the individual consumption of 8.05×10^{-5} mg/kg/day and 1.71×10^{-3} mg/kg/day Turpentine (CAS RN 9005-90-7) and Turpentine oil (CAS RN 8006-64-2) respectively, for the US population established in Fenaroli's Handbook of Flavor Ingredients (personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2017; unreferenced).

Turpentine oil may also be a component in incidental food additives (cleaners). However, there is no potential for direct food contact since use of the cleaners is followed by a potable water rinse (personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2017; unreferenced).

To evaluate the potential for worst case exposure to turpentine from cosmetics, a sentinel scenario was selected based on a combination of use frequencies and reported concentrations of turpentine/turpentine oil in a product. The highest daily oral exposure

to turpentine is expected to occur from the use of a lip balm with reported upper concentration of 0.1% turpentine/turpentine oil. Systemic exposure by the oral route for lip balm ranged from 2.90 x 10^{-4} to 4.00 x 10^{-4} mg/kg bw/day (all age groups). In addition, systemic exposure by the dermal and inhalation routes were calculated for shoe polish cream containing 10% turpentine (adult-9.85 x 10^{-2} mg/kg bw/day), paint thinner for oil-based paints containing 100% turpentine (adult-2.65 mg/kg bw/day), paint remover containing 100% turpentine (adult-4.37 x 10^{1} mg/kg bw/day), and car wax containing 10% turpentine (adult-2.93 x 10^{-1} mg/kg bw/day). This data and all its parameters are summarized in Appendix G, Tables G-1 to G-3).

Turpentine oil was also reported to be used as a non-medicinal ingredient in a topical medicated vapour product at 4.68% and a topical counterirritant product at 25% (personal communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau, Health Canada, 2018 and 2019; unreferenced). Systemic exposure by the dermal and inhalation route ranged from 5.11 to 7.02 mg/kg bw/day and 2.06 to 4.86 mg/kg bw/day for the medicated vapour product and counterirritant product, respectively.

8.4.2.2 Health effects assessment

No classification of the health effects of turpentine and turpentine oils by national or international regulatory agencies were identified.

The US FDA indicates that turpentine and turpentine oils may be safely used as a flavouring agent in food when used in the minimum quantity required to produce the intended effect (US FDA 2017c).

Several short-term and repeated dose animal studies have been identified for turpentine oil. However, the studies are considered scientifically inadequate for inclusion in the present assessment given they are missing key information including exposure concentrations, exposure methods, test material identity, control animals or multiple doses.

Turpentine/turpentine oil underwent a screening-level hazard characterization by the US EPA in 2010 as a sponsored chemical (part of the Bicyclic Terpene Hydrocarbons category) under the HPV Challenge Program (US EPA 2010). In the review, no short-term, chronic, reproductive/developmental toxicity or carcinogenicity studies were identified for turpentine/turpentine oil itself. Rather, points of departure were established for turpentine/turpentine oil based on read across values from alpha-pinene (NOAEC=50 ppm, LOAEC=100 ppm) and camphene (oral NOAEL=250 mg/kg bw/day, LOAEL=1000 mg/kg bw/day). No concerns were highlighted for in vitro bacterial genotoxicity.

Turpentine/turpentine oil was found to be negative for bacterial mutagenicity, negative for in vitro mammalian gene mutation and negative for in vitro chromosomal aberrations

in human lymphocytes, all with and without exogenous metabolic activation (ECHA 2018b).

The effect of short-term inhalation exposure to turpentine on eight male volunteers exposed to 450 mg/m^3 of the turpentine mixture comprised of alpha-pinene, beta-pinene and delta-3-carene(10:1:5) in an exposure chamber on four different occasions during a two week period for a total of twelve hours was investigated (Johard et al. 1993). Bronchoalveolar lavage was assessed before and after the exposures as an indicator of an inflammatory response. Twenty hours following the final exposure, the number of macrophages and mast cells in the bronchial lavage fluid were significantly higher than before the exposures occurred, indicating an acute alveolar cellular response.

In another similar study, eight volunteers were exposed to 450 mg/m^3 turpentine in an exposure chamber for two hours while doing light exercise (Falk-Filipsson 1996). Participants noted significantly increased levels of discomfort to the throat or airways following turpentine exposure compared to control exposures. Significant increases in airway resistance were also noted 30 min after the exposure to turpentine had ended. Small, but non-significant increases in discomfort to the nose were observed following turpentine exposure. In terms of symptoms relating to the CNS, no significant differences were noted following exposure to turpentine relative to control exposures.

In order to further inform the risk assessment, the hazard information available for alpha-pinene (44-94%), beta-pinene (0.9-30%), limonene (0.7-25%), and camphene (1-15%), as the main components of turpentine/turpentine oil have been considered.

Hazard assessment of main components

Alpha- and Beta-Pinene

Alpha- and beta-pinene were reviewed by the US EPA in 2010 as a sponsored chemical (part of the Bicyclic Terpene Hydrocarbons category) under the HPV Challenge Program (US EPA 2009), which established a NOAEC of 50 ppm and LOAEC of 100 ppm. Further information on the health effects of alpha-pinene and beta-pinene are provided in the Health effects assessment section of alpha-pinene (Section 8.3.2.2).

Limonene

Limonene can be considered a substance of fairly low toxicity. Further information on the health effects of limonene are provided in the Potential to cause harm to human health section for sweet orange oil (Section 8.1.2).

Camphene

In an oral 28 day repeated dose study for camphene, male and female rats were administered orally to 0, 62.5, 250 and 1 000 mg/kg bw/day camphene and a NOAEL of 250 mg/kg bw/day and a LOAEL of 1 000 mg/kg bw/day were determined based on

increased liver weights and hepatocyte vacuolization in both male and female rats at 1 000 mg/kg bw/day (US EPA 2010).

8.4.2.3 Characterization of risk to human health

Chronic Exposure Durations:

Inhalation:

Little or no health effects data is available for turpentine /turpentine oil via the inhalation route. Therefore, inhalation data for alpha-pinene, the main component comprising 44-94% of turpentine/turpentine oil was considered for this point of departure. The critical effect level is a NOAEC of 50 ppm (equivalent to $NOAEC_{adj}$ = 49.73 mg/m^3 or $NOAEL_{adj}$ = 66 mg/kg bw/day when corrected for an exposure of 6 hours per day and 5 days per week, see Appendix F-6 for details on the dose conversion) as identified in the 14 week NTP study (NTP 2016). This was based on significantly increased incidence of transitional epithelium hyperplasia in the bladder of male and female mice at 100 ppm or higher concentration (equivalent to 133 mg/kg bw/day when corrected for an exposure of 6 hours per day and 5 days per week) and decreased sperm cauda in male mice at and above 100 ppm.

Oral:

The US EPA used read-across data from camphene and assigned turpentine /turpentine oil an oral NOAEL of 250 mg/kg bw/day based on a repeated-dose study with camphene. However, turpentine/turpentine oil contains camphene only in concentrations from 1-15%, while it contains alpha-pinene at concentrations of 44-94%. Given the availability of quality data for alpha-pinene and further that the systemic NOAEL for alpha-pinene (equivalent to $NOAEL_{adj}$ of 66 mg/kg bw/day) was lower than that for camphene (250 mg/kg bw/day), the inhalation NOAEC of 50 ppm (adjusted to 66 mg/kg bw/day) identified for alpha-pinene above was used for quantification of risk along with route-to-route extrapolation as it yields a more conservative point of departure than that of camphene. The calculation assumes that absorption by the oral and inhalation routes are equivalent.

Dermal:

No health effects data exists for turpentine/turpentine oil via the dermal route. Consequently, the inhalation NOAEC of 50 ppm (equivalent to 66 mg/kg bw/day when corrected for an exposure of 6 hours per day and 5 days per week) as identified above was used for characterization of risk along with route-to-route extrapolation. A dermal absorption value of 20% (occluded conditions) or 4% (unoccluded conditions) was used for the route-to-route extrapolation.

Short-Term Exposure Durations:

There was no health effects data available for turpentine/turpentine oil. Therefore, data for alpha-pinene, the main component of turpentine/turpentine oil was considered. The critical effect level NOAEC of 200 ppm (equivalent to $NOAEL_{adj}$ = 222 mg/kg bw/day or $NOAEC_{adj}$ = 199 mg/m^3 when corrected for an exposure of 6 hours per day and 5 days per week, see Appendix F-6 for details on the dose conversion) as identified in the 2 week range-finding NTP study (NTP 2016) was used for this point of departure. This was based on significantly decreased body weight in female rats and mice, and increased relative liver and kidney weights in rats and mice at 400 ppm. Route-to-route extrapolation was used for the oral and dermal routes of exposure.

Since the critical effects from the 14-week and 2-week range-finding study inhalation study were systemic in nature (i.e. transitional epithelium hyperplasia in the bladder and decreased sperm cauda in the 14-week study and decreased body weight and increased relative liver and kidney weights in the 2-week study), and are expected to occur following repeated exposures, it was considered appropriate to calculate inhalation exposures on a per kg basis and compare the inhalation exposure to an adjusted systemic dose from the inhalation study. Systemic inhalation exposures were calculated using the 24-hour time weighted average air concentration from the exposure scenario and standard daily inhalation rates and body weights as outlined in Health Canada, 1998.

For risk characterization purposes, based on the literature review, it was assumed that the main components of turpentine oil were alpha-pinene and beta-pinene. Since alpha-pinene was used as a read-across analogue for beta-pinene, the hazard of alpha-pinene was considered to be equivalent to turpentine/turpentine oil.

Exposure from use of turpentine oil in food and lip balm was considered to be chronic in nature, as consumers generally use these commodities and/or products on a daily basis. However, exposure from the use of turpentine oil in shoe polish cream, paint thinner or remover, furniture paste, car wax and as a non-medicinal ingredient in a topical medicated vapour product was considered to be short-term in duration, as consumers generally use these products on an intermittent and infrequent basis throughout the year. Exposure estimates, critical effect levels and resulting margins of exposure for chronic and short-term scenarios are presented in Table 8.4-2 and 8.4-3, respectively.

Table 8.4-2. Relevant chronic exposure estimates, critical effect levels and resulting margins of exposure, for turpentine/turpentine oil

Exposure Scenario [a]	**Systemic Exposure (mg/kg bw/day)**	**MOE[b]**
Food flavoring (dietary intake) – oral	8.05×10^{-5} -1.709×10^{-3} (6 months and above)	38 619 - 819 876 (6 months and above)

Exposure Scenario [a]	Systemic Exposure (mg/kg bw/day)	MOE[b]
Lip balm (0.1%)	0.0029 - 0.004 (all age groups except infants)	16 500 - 22 759 (all age groups except infants)

[a] Exposure scenario parameters and calculations for turpentine/turpentine oil outlined in Appendix G
[b] Margin of exposure was calculated using the critical effect level ($NOAEL_{adj}$ = 66 mg/kg bw/day) based on transitional epithelium hyperplasia in the bladder (male and female) and decreased sperm cauda (male) from the 14-week inhalation study of alpha-pinene in mice.

Table 8.4-3. Relevant short-term exposure estimates, critical effect levels and resulting margins of exposure, for turpentine/turpentine oil

Exposure Scenario[a]	Systemic Exposure (mg/kg bw/day)	MOE[b]
Systemic exposure by the dermal and inhalation route from shoe polish (10%)[c]	9.85×10^{-2} (adult)	2 254 (adult)
Systemic exposure by the dermal and inhalation route from paint thinner (100%)[c]	2.65 (adult)	**84** (adult)
Systemic exposure by the dermal and inhalation route from paint remover (100%)[c]	4.37×10^{1} (adult)	**5** (adult)
Systemic exposure by the dermal and inhalation route from furniture paste wax (5%)[c]	6.67×10^{-2} (adult)	3 328 (adult)
Systemic exposure by the dermal and inhalation route from car wax (10%)[b]	2.93×10^{-1} (adult)	757 (adult)
Systemic exposure by the dermal and inhalation route from non-medicinal ingredient in topical medicated vapour product (2%)[d]	5.11 – 7.02 (adult-toddler)	**32 - 43** (toddler–adult)
Systemic exposure by the dermal and inhalation route from non-medicinal ingredient in counterirritant product (25%)[d]	2.06 – 4.86 (adult-toddler)	**46 - 108** (toddler–adult)

[a] Exposure scenario parameters and calculations for turpentine/turpentine oil outlined in Appendix G.
[b] Margin of exposure was calculated using the critical effect level ($NOAEL_{adj}$ = 222 mg/kg bw/day) based on decreased body weights and increased relative liver and kidney weights from the 2-week range-finding inhalation study of alpha-pinene in mice and rats.
[c] Dermal absorption factor of 4% (unoccluded conditions).
[d] Dermal absorption factor of 20% (occluded conditions).

The margin of exposure between the critical effect level and the estimate of daily exposure to turpentine oil for paint thinner and remover, and non-medicinal ingredient in topical medicated vapour product and a counterirritant product ranged from 5 to 108. These margins of exposure are considered potentially inadequate to account for uncertainties in the health effects and exposure databases.

A recent analysis of the volatile fraction of turpentine oils available at Canadian stores indicated that some marketed turpentines/turpentine oils may contain limited alpha-pinene, but appreciable concentrations of alpha and gamma-terpinene (HC 2019). Considering the hazard profile of alpha and gamma-terpinene described previously in the assessment of mandarin oil (Section 8.2.2.2), a similar risk characterization outcome would be expected for turpentine oils with this different composition as compared to those comprised primarily of alpha-pinene.

For all other scenarios, the margins of exposure between the critical effect level and the estimate of exposure for scenarios listed in Table 8.4-2 and 8.4-3 are considered adequate to account for uncertainties in the health effects and exposure databases.

8.4.2.4 Uncertainties in evaluation of risk to human health

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

Table 8.4-4. Sources of uncertainty in the risk characterization for turpentine/turpentine oil

Key source of Uncertainty	Impact
Exposure	
Combining both the dermal and inhalation routes, and the use of conservative assumptions to calculate exposure from each route of exposure, may result in conservative estimates.	+
Inhalation estimates for turpentine oil in products is very dependent upon factors such as room volume, ventilation rates, time spent in area of application and calculation of the time-weighted average. Each of these parameters has variability and uncertainty. Conservative assumptions were used.	+
There is a degree of uncertainty in extrapolating the dermal absorption data from linalool and citronellol to turpentine/turpentine oil; however, as all the acyclic/monocyclic/bicyclic monoterpenes and constituents thereof have similar physical-chemical properties, the dermal absorption of these compounds is expected to be similar.	+/-
Route-to-route extrapolation for turpentine oil was carried out for dermal and oral scenarios in comparing to an effect level from an inhalation study.	+/-
The concentration of the main components in turpentine/turpentine oil differs depending on the origin of the plant, its species, temperature, soil, and geography. Therefore, the composition of turpentine/turpentine oil present in products available to consumers is unknown, which represents an uncertainty in the assessment.	+/-
Hazard	
There are no short term, chronic, reproductive/developmental toxicity or carcinogenicity studies were identified for turpentine/turpentine oil.	+/-
There are no adequate animal studies examining the repeated-dose toxicity of turpentine oil for any of the relevant routes of exposure (i.e., dermal, oral,	+/-

Key source of Uncertainty	Impact
inhalation). Hazard data from the main component, alpha-pinene, was used to inform the health effects assessment, where applicable.	
The use of a range finding study to characterize risk from acute/short-term exposure scenarios may potentially underestimate hazard as it did not contain a full analysis of toxicity data.	-

+ = 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.

8.5 Fir oil

8.5.1 **Sources and uses**

Fir oil is a naturally occurring substance prepared by steam distillation of the needles and twigs of *Abies balsamea* found in North America, particularly Canada and the northern US (Burdock 2010).

Based on information submitted pursuant to a section 71 survey under CEPA (Canada 2012), 100 kg of fir oil was manufactured in Canada in 2011 (Environment Canada 2013). There were no reports of import above the reporting threshold of 100 kg for fir oil in the same calendar year (Environment Canada 2013).

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, fir oil is used in approximately 90 cosmetic products in Canada at concentrations ranging from <0.1%-100% (personal communication, emails from the Consumer Product Safety Directorate, 2017; unreferenced). Some of the product types include body lotion, massage products, cleansers, fragrance, make-up, hair care, and bath products. The majority of products (>60%) contain fir oil at a concentration range of 1% or less.

Fir oil is also listed as a fragrance ingredient used in consumer goods by the International Fragrance Association (IFRA 2017).

Information obtained pursuant to a section 71 survey under CEPA also reported uses as an odor agent in cleaning and furnishing care products, laundry and dishwashing products, apparel and footwear care as well as automotive care products and lubricants/greases (Environment Canada 2013). Information from the American Cleaning Institute's (ACI) website indicated potential use of fir oil as a fragrance in household all-purpose cleaners (ACI 2017).

Fir oil is used in alcoholic and non-alcoholic beverages, baked goods, candy, frozen dairy and gelatins/puddings (Burdock 2010). Fir oil is listed in the US FDA Substances Added to Food inventory and in the Food Chemicals Codex as a flavouring agent (US FDA 2018; FCC 2018). No definitive information is available concerning the potential use of fir oils as a food flavouring agent in Canada however since the substance is

known to be used as a food flavouring agent in the US, it is possible that it is present as a flavouring agent in foods sold in Canada.

Additional uses for fir oil are listed in Table 8.5-1.

Table 8.5-1. Additional uses in Canada for fir oil

Use	Details
Food flavouring[a]	Reported uses in alcoholic and non-alcoholic beverages, baked goods, candy, frozen dairy and gelatins/puddings (Burdock 2010).
Natural Health Products Ingredients Database[b]	Flavor enhancer and fragrance ingredient.
Licensed Natural Health Products Database being present as a medicinal or non-medicinal ingredient in natural health products in Canada[b]	MI, NMI
Notified to be present in cosmetics, based on notifications submitted under the *Cosmetic Regulations* to Health Canada[c]	Skin and hair care products, fragrances, and deodorants.
Formulant in pest control products registered in Canada[d]	Formulant

Abbreviations: MI, medicinal ingredient; NMI, non-medicinal ingredient.

[a] Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[b] Email communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[c] Email communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[d] Email communication from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau; unreferenced

8.5.2 **Potential to cause harm to human health**

8.5.2.1 Exposure assessment

In consideration of the low quantities of the substance reported to be used in Canada (Environment Canada 2013), an impact on human health from exposure to fir oil from environmental media is not expected.

The main components of fir oil, beta-pinene (~28-56%) and alpha-pinene (~6-26%) have been detected frequently in indoor and outdoor air (HC 2010a, b, 2012, 2013). Similar to alpha-pinene, beta-pinene is a natural constituent of coniferous trees and is emitted from vegetation and wood products. In general, detected levels of beta-pinene are lower than that of alpha-pinene and are considered to be addressed as part of the alpha-pinene assessment.

Dietary exposure of Canadians to fir oil when used as a food flavouring agent was estimated based on the individual consumption of 1.58×10^{-3} mg/kg bw/day for the US population established by Fenaroli's Handbook of Flavor Ingredients (personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2017; unreferenced).

To evaluate the potential for exposure by the dermal route of administration to fir oil from cosmetics, sentinel scenarios were selected based on a combination of use frequencies and reported concentrations of fir oil in these products. These scenarios represented the highest exposure by the dermal route of administration, relative to other dermally applied cosmetics and natural health products based on identified products reported to contain the substance. Exposure to fir oil from the use of a body moisturizer, massage oil, and face moisturizer were considered to be the sentinel scenarios to estimate daily exposure by the dermal route of administration. This data is summarized in Appendix H (Tables H-1 to H-3).

The highest daily exposure to fir oil is expected to occur from the use of a body moisturizer with reported upper concentration of 1% fir oil. Systemic exposure by the dermal and inhalation route for body moisturizer (assuming 20% dermal absorption) ranged from 0.291 to 0.535 mg/kg bw/day (all age groups). In addition, systemic exposure by the dermal and inhalation route for massage oil (3%) and face moisturizer (3%) ranged from 0.0638 to 0.295 mg/kg bw/day (adult – infants), and 0.238 to 0.416 mg/kg bw/day (12-19 years – adult), respectively.

Exposure by the inhalation route to fir oil may result from the use of spray perfume (100% fir oil) and air freshener/wax melt (1-5% fir oil). Systemic exposure by the inhalation route from a perfume containing 100% fir oil ranged from 0.0889 to 0.0434 mg/kg bw/day (adults to 5 year-olds) (0.19 mg/m^3) while exposure by the inhalation route from the air freshener/wax melt ranged from 0.165 to 0.432 mg/kg bw/day (adult-toddler) (0.72 mg/m^3) (full calculation parameters in Appendix-H, Tables H-3 to H-5).

Fir oil was also reported to be used as a non-medicinal ingredient in liquid cold medication at a concentration of 0.27% (personal communication with NNHPD, Jan 2018, unreferenced). Systemic exposure by the oral route ranged from 1.14 to 2.61 mg/kg bw/day (children three years and above to adult). In addition, fir oil was reported to be present in a chest balm product at an upper concentration of 3% (personal communication with Consumer Product Safety Directorate, 2019, unreferenced). Systemic exposure by the dermal and inhalation routes ranged from 0.822 to 1.11 mg/kg bw/day (adult-infant) (full calculation parameters in Appendix-H, Table H-5).

8.5.2.2 Health effects assessment

No classification of the health effects of fir oils by national or international regulatory agencies was identified.

The US FDA indicates that fir oils may be safely used as a flavouring agent in food when used in the minimum quantity required to produce the intended effect (US FDA 2017c).

Limited toxicological information is available for fir oil. Fir oil was reviewed in 2007 by the US EPA as part of a Biopesticides Registration Action Document for Balsam fir oil. Acceptable acute toxicity guideline studies (e.g., acute oral, dermal, inhalation toxicity) were received for Balsam fir oil, and as no significant effects were identified, the requirements for further studies (e.g. repeated dose, immunotoxicity) were waived (US EPA 2007).

No studies regarding the genotoxicity, carcinogenicity or reproductive/developmental toxicity of fir oil have been identified in the literature.

In order to inform the risk assessment, the hazard information available for the main components of fir oil, beta-pinene (28-56%), alpha-pinene (6-26%), and limonene (2-16%), have been considered.

Alpha- and beta-pinene were reviewed by the US EPA in 2010 as a sponsored chemical (part of the Bicyclic Terpene Hydrocarbons category) under the HPV Challenge Program (US EPA 2009), which established a NOAEC of 50 ppm and LOAEC of 100 ppm. Further information on the health effects of alpha-pinene are provided in the Health effects assessment section for alpha-pinene (Section 8.3.2.2).

Limonene can be considered a substance of fairly low toxicity. Further information on the health effects of limonene are provided in the Potential to cause harm to human health section for sweet orange oil (Section 8.1.2).

8.5.2.3 Characterization of risk to human health

Chronic exposure durations:

Inhalation:

In the absence of health effects information about fir oil or it's main component beta-pinene, inhalation data for alpha-pinene, which comprises 6-26% of fir oil, which was used by the US EPA to read across to beta-pinene (US EPA 2010) was considered for this point of departure. A NOAEC of 50 ppm (equivalent to 49.73 mg/m^3 or 66 mg/kg bw/day when corrected for an exposure of 6 hours per day and 5 days per week, see Appendix F-6 for details on dose conversions) was identified in the 14-week NTP study (NTP 2016). This was based on significantly increased incidence of transitional epithelium hyperplasia in the bladder of male and female mice at and above 100 ppm (equivalent to 99.46 mg/m^3 when corrected for an exposure of 6 hours per day and 5 days per week) and decreased sperm cauda in male mice at and above 100 ppm.

Oral and Dermal:

No health effects data exists for fir oil, or its main component beta-pinene, via the oral or dermal routes. Consequently, oral data for camphene which is used by the US EPA to read across to beta-pinene (US EPA 2010) can be considered for this point of departure. The critical effect level is a NOAEL of 250 mg/kg bw/day as identified in a 28 day rat study. The effect level is based on increased liver weights and vacuolization of hepatocytes at 1 000 mg/kg bw/day.

However, the NOAEL for alpha-pinene (equivalent to 66 mg/kg bw/day when corrected for exposure of 6 hours per day and 5 days per week, see Appendix F-6 for details on dose conversions) is a more conservative point of departure than that for camphene (250 mg/kg bw/day) and thus was used for characterization of risk along with route-to-route extrapolation. The calculation assumes that absorption by the oral and inhalation routes are equivalent for the inhalation to oral extrapolation and that dermal absorption is 20% (occluded) or 4% (unoccluded) for the inhalation to dermal extrapolation.

Short-Term exposure durations:

Inhalation/Oral/Dermal:

There was no health effects data available for fir oil. Therefore, data for alpha-pinene, one of the components of fir oil was considered. The critical effect level NOAEC of 200 ppm (equivalent to $NOAEL_{adj}$ = 222 mg/kg bw/day or $NOAEC_{adj}$ = 199 mg/m^3 when corrected for an exposure of 6 hours per day and 5 days per week see Appendix F-6 for details on dose conversion) as identified in the 2 week range-finding NTP study (NTP 2016) was used for this point of departure. This was based on significantly decreased body weight in female rats and mice, and increased relative liver and kidney weights in rats and mice at 400 ppm. Route-to-route extrapolation was used for the oral and dermal routes of exposure.

Since the critical effects from the 14-week and 2-week range-finding study inhalation study were systemic in nature (i.e. transitional epithelium hyperplasia in the bladder and decreased sperm cauda in the 14-week study and decreased body weight and increased relative liver and kidney weights in the 2-week study), and are expected to occur following repeated exposures, it was considered appropriate to calculate inhalation exposures on a per kg basis and compare the inhalation exposure to an adjusted systemic dose from the inhalation study. Systemic inhalation exposures were calculated using the 24-hour time weighted average air concentration from the exposure scenario and standard daily inhalation rates and body weights as outlined in Health Canada, 1998.

Given that the main components of fir oil are beta-pinene and alpha-pinene, and that alpha-pinene was used as a read-across analogue for beta-pinene, the toxicity of alpha-pinene was considered to be equivalent to fir oil.

All of the sentinel exposure scenarios were considered to be chronic in duration, except for the use of fir oil as a non-medicinal ingredient in a liquid cold medication and its presence in a chest balm product (3%), which were considered to be short-term in duration. Liquid cold medications and chest balms are used infrequently throughout the year, and it is expected that they would only be used for a maximum duration of 5 to 7 days each time.

Exposure estimates, critical effect levels and resulting margins of exposure for chronic and short-term scenarios are presented in Table 8.5-2 and Table 8.5-3, respectively.

Table 8.5-2. Relevant chronic exposure estimates, critical effect levels and resulting margins of exposure, for fir oil

Exposure Scenario[a]	Systemic Exposure (mg/kg bw/day)	MOE[b]
Food flavouring (dietary intake) - oral	1.58×10^{-3} (6 months and above)	41 772 (6 months and above)
Systemic exposure by the dermal and inhalation route from body moisturizer (1%)[c]	$2.91 \times 10^{-1} – 5.35 \times 10^{-1}$ (adult-infant)	123 - 227 (infant-adult)
Systemic exposure by the dermal and inhalation route from massage oil (3%)[d]	$6.38 \times 10^{-2} – 2.95 \times 10^{-1}$ (adult-infant)	224 - 1 035 (infant–adult)
Systemic exposure by the dermal and inhalation route from face moisturizer (3%)[d]	$2.38 \times 10^{-1} – 4.16 \times 10^{-1}$ (12 to 19 yrs–adult)	159 - 278 (adult–12 to 19 yrs)
Systemic exposure by the inhalation route from fragrance product (100%)	$8.89 \times 10^{-2} – 4.34 \times 10^{-2}$ (adult-5 to 11 yrs)	743 - 1 520 (adult–5 to 11 yrs)
Systemic exposure by the inhalation route from air freshener (wax melt) (5%)	$1.65 \times 10^{-1} – 4.32 \times 10^{-1}$ (adult-toddler)	153 - 401 (toddler–adult)

[a] Exposure scenario parameters and calculations for fir oil outlined in Appendix H.
[b] Margin of exposure was calculated using the critical effect level ($NOAEL_{adj}$ = 66 mg/kg bw/day) based on transitional epithelium hyperplasia in the bladder (male and female) and decreased sperm cauda (male) from the 14-week inhalation study of alpha-pinene in mice.
[c] Assuming dermal absorption of 20% (occluded).
[d] Assuming dermal absorption of 4% (unoccluded).

Table 8.5-3. Relevant short-term exposure estimates, critical effect levels and resulting margins of exposure for fir oil

Exposure Scenario	Exposure (mg/kg bw/day)	MOE[a]
Systemic exposure by the oral route from non-medicinal ingredient in liquid cold medication (0.27%)	1.14 - 2.61 (adult-children 3+)	85 - 195 (children 3^{+}- adult)

Exposure Scenario	Exposure (mg/kg bw/day)	MOE[a]
Systemic exposure by the dermal and inhalation route from chest balm product (3%)	8.22×10^{-1} – 1.11 (adult-infant)	201 - 270 (infant–adult)

[a] Margin of exposure was calculated using the critical effect level ($NOAEL_{adj}$ = 222 mg/kg bw/day) based on decreased body weights and increased relative liver and kidney weights from the 2-week range-finding inhalation study of alpha-pinene in mice and rats.

The margin of exposure between the critical effect level and the estimate of exposure to fir oil in a liquid cold medication was 85 for children aged 3 years and older, which is considered adequate to account for uncertainties in the health effects and exposure databases. In addition, the margin of exposure between the critical effect level and the estimate of exposure to fir oil in a chest balm product when used according to label directions (i.e. one application per day) ranged from 201 to 270, which is considered adequate to account for uncertainties in the health effects and exposure databases.

For all other scenarios, the margins of exposure between the critical effect level and the estimate of exposure ranged from 123 to 41 772, which are considered adequate to account for uncertainties in the health effects and exposure databases.

8.5.2.4 Uncertainties in evaluation of risk to human health

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

Table 8.5-4. Sources of uncertainty in the risk characterization for fir oil

Key source of Uncertainty	Impact
Exposure	
Inhalation estimates for fir oil in products is very dependent upon factors such as room volume, ventilation rates, time spent in area of application and calculation of the time-weighted average. Each of these parameters has variability and uncertainty. Conservative assumptions were used.	+
There is a degree of uncertainty in extrapolating the dermal absorption data from linalool and citronellol to fir oil; however, as all the acyclic/monocyclic/bicyclic monoterpenes and constituents thereof have similar physical-chemical properties, the dermal absorption of these compounds is expected to be similar.	+/-
Route-to-route extrapolation for fir oil was carried out for dermal and oral scenarios in comparing to an effect level from an inhalation study.	+/-
The composition of the main components in fir oil differs depending on the origin of the plant, its species, temperature, soil, and geography. Therefore, the composition of fir oil present in products available to consumers is unknown, which represents an uncertainty in the assessment.	+/-
Hazard	
There are no chronic, reproductive/developmental or carcinogenicity animal studies for all routes of exposure.	+/-

Key source of Uncertainty	Impact
There were no animal studies examining the repeated-dose toxicity of fir oil for any of the relevant routes of exposure (i.e., dermal, oral, inhalation). Hazard data from a component of fir oil, alpha pinene, was used to inform the health effects assessment.	+/-
The use of a range-finding study to characterize risk from acute/short-term exposure scenarios may potentially underestimate hazard as it did not contain a full analysis of toxicity data.	-

+ = 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.

8.6 Pine oil

8.6.1 Sources and uses

Pine oil is a naturally occurring substance that is derived from the steam distillation of various *Pinus* spp., primarily *Pinus sylvestris* native to the Baltic States*, Pinus mugo* native to the Swiss Alps and *Pinus palustris* which is native to North America (Rose 2009).

Based on information submitted pursuant to a section 71 survey under CEPA (Canada 2012), between 100 and 1000 kg of pine oil were manufactured in Canada in 2011 (Environment Canada 2013). Between 100 000 and 1 000 000 kg of pine oil was imported into Canada during the same calendar year (Environment Canada 2013).

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, pine oil is used in greater than 65 cosmetic products in Canada at concentrations ranging from <0.1%-100% (personal communication, emails from the Consumer Product Safety Directorate, 2017; unreferenced). Some of the product types reported include body lotion, massage products, cleansers, fragrance, make-up, hair care, and bath products. The majority of products (>85%) contain pine oil at a concentration range of 1% or less.

Pine oil is listed as a fragrance ingredient used in consumer goods by the International Fragrance Association (IFRA 2017).

Information obtained pursuant to a section 71 survey under CEPA also reported uses as a solvent or odor masking agent in products related to personal care products, cleaning and furnishing care, laundry and dishwashing, air care, as well as automotive products, lubricants/greases and paints/coatings (Environment Canada 2013). Pine oil was also listed in household products (MSDS 2008; MSDS 2015). Information from the American Cleaning Institute's (ACI) website indicates potential use of pine oil in household cleaning products including all-purpose cleaners and dish and laundry care products (ACI 2017).

Pine oil has reported uses in food including alcoholic and non-alcoholic beverages, baked goods, frozen dairy, gelatins/puddings and candy (Burdock 2010). Pine oil (CAS RN 8002-09-3) does not have any specific food status in the US or Europe; however, pine bark, white oil (CAS 977089-62-5), pine needle, dwarf oil (CAS 8000-26-8), pine scotch oil (CAS 8023-99-2), pine tar oil (CAS 977009-97-4) and pine, white oil (CAS 977019-44-5) are permitted in the US as flavouring substances (US FDA 2018). No definitive information is available concerning the potential use of pine oil as a food flavouring agent in Canada however since the substance is known to be used as a food flavouring agent in the US, it is possible that it is present as a flavouring agent in foods sold in Canada.

Additional uses for pine oil are listed in Table 8.6-1.

Table 8.6-1. Additional uses in Canada for pine oil

Use	Details
Food flavouring[a]	Reported uses in alcoholic and non-alcoholic beverages, baked goods, frozen dairy, gelatins/puddings, and candy (Burdock 2010).
Incidental additives[a]	Component in can end cements, coatings for floors.
Drug Products Database[b]	NMI (ingredient in human and disinfectant drugs)
Natural Health Products Ingredients Database[c]	MI, NMI
Licensed Natural Health Products Database being present as a medicinal or non-medicinal ingredient in natural health products in Canada[c]	MI, NMI
Notified to be present in cosmetics, based on notifications submitted under the *Cosmetic Regulations* to Health Canada[d]	Skin and hair care products, deodorants, and massage products.

Abbreviations: MI, medicinal ingredient; NMI, non-medicinal ingredient.

[a] Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[b] Email communication from Therapeutic Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[c] Email communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced

[d] Email communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau; unreferenced

8.6.2 **Potential to cause harm to human health**

8.6.2.1 Exposure assessment

In considering environmental media, alpha-pinene (which makes up 12-69% of pine oil) was used to inform its partitioning to the environment. Due to its high vapour pressure (633 Pa), alpha-pinene is expected to partition almost completely to air (Kim et al. 2016). In addition, due to its low water solubility (2.49 mg/L) and its very high Henry's law constant 0.30 atm-m^3/mol), alpha-pinene is expected to volatilize rapidly from water surfaces.

No air monitoring data was found for pine oil; however its major constituent alpha-pinene has been addressed in Section 8.3.2.1.

Dietary exposure of Canadians to pine oil when used as a food flavouring agent was estimated based on the individual consumption of 2.97×10^{-4} mg/kg bw/day for the US population as established in Fenaroli's Handbook of Flavor Ingredients (personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2017; unreferenced).

Pine oil may be present as components in certain food packaging materials such as cements used for sealing can ends, and incidental additives such as coatings for floors (no direct food contact). The exposure to pine oil from food packing materials and incidental additives was estimated to be negligible (personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2017; unreferenced).

To evaluate the potential for exposure by the dermal route of administration to pine oil from cosmetics, sentinel scenarios were selected based on a combination of use frequencies and reported concentrations of pine oil in these products. These scenarios represented the highest exposure by the dermal route of administration, relative to other dermally applied cosmetics and natural health products based on identified products reported to contain the substance. Exposure to pine oil from the use of a body moisturizer and massage product were considered to be the sentinel scenarios to estimate daily exposure by the dermal route of administration. This data is summarized in Appendix I (Tables I-1and I-2).

The highest daily exposure to pine oil is expected to occur from the use of a body moisturizer with reported concentration of 0.3% pine oil. Systemic exposure by the dermal and inhalation route for body moisturizer (assuming 20% dermal absorption) ranged from 7.24×10^{-2} to 1.61×10^{-1} mg/kg bw/day (adult-infant). Systemic exposure by the dermal and inhalation route from a massage product (maximum 1% pine oil) ranged from 2.13×10^{-2} to 9.82×10^{-2} mg/kg bw/day (infant-adult).

Exposure by the inhalation route to pine oil may result from the use of spray perfume (100% pine oil). For a perfume containing 100% pine oil, exposure from the inhalation

route ranged from 8.89 x 10^{-2} – 4.34 x 10^{-2} mg/kg bw/day (adults to 5 year-olds) (0.19 mg/m^3) (full calculation parameters in Appendix-I, Tables I-3). In addition, systemic exposure by the dermal, inhalation and non-dietary ingestion routes to a toddler coming into contact with cleaned floor (containing 5% pine oil) was calculated to be 2.13 x 10^{-1} mg/kg bw/day while systemic exposure by the dermal and inhalation route for an adult mixing, loading, and applying an all-purpose liquid floor cleaner (also containing 5% pine oil) was calculated to be 8.81 x 10^{-2} mg/kg bw/day. Systemic exposure by the inhalation route from an automatic toilet bowl cleaner (containing 10% pine oil) was calculated to range from 6.63 x 10^{-2} – 1.74 x 10^{-1} mg/kg bw/day (adult to toddler) (2.90 x 10^{-2} mg/m^3). The data and all its parameters are summarized in Appendix I, Tables I-4 to I-5).

Pine oil was also reported to be used as a non-medicinal ingredient in natural health products at a concentration of 4 mg/mL (personal communication with NNHPD, Jan 2018, unreferenced). Systemic exposure by the oral route ranged from 2.82 to 3.37 mg/kg bw/day (adult to adolescent).

A therapeutic product administered by the topical route containing 8.1% pine oil as non-medicinal ingredient was listed in an antiseptic liquid (email communication from Therapeutics Product Directorate to Existing Substances Risk Assessment Bureau; unreferenced). However, exposure by the dermal route to pine oil from this product is expected to be less than the highest estimates of exposure from use of cosmetics.

8.6.2.2 Health effects assessment

Hazard assessment of pine oil

No classification of the health effects of pine oil by national or international regulatory agencies were identified.

Limited toxicological information is available for pine oil.

Two short-term dermal studies evaluated the effects of exposure to pine oil in the rat. The details of these studies were not available for independent evaluation; however, summaries were published in the California Department of Food and Agriculture, Medical Toxicology Branch, Summary of Toxicology Data for pine oil (1998), as well as in the US EPA's Reregistration Eligibility Decision for Pine Oil (US EPA 2006). In the first study, adverse effects were not observed when a pine oil blend (test material undefined) was administered neat to rat skin (10/sex/group) for 5 days/week for 90 days at 0, 50, 113 or 226 mg/kg/day. A NOAEL of greater than 226 mg/kg/day was determined. In the second one, a 14-day dermal exposure in rats showed no adverse effects up to 940 mg/kg/day (US EPA 2006).

In a developmental study, pregnant rats (25/group) were administered 0, 50, 600 or 1 200 mg/kg bw/day of a pine oil blend by gavage during gestational days 6 to 15 (US EPA 2006). At 600 mg/kg bw/day, a significant decrease of fetal weight in males was

observed as well as an increase of incompletely ossified pubes and/or ischia in pups. No maternal effect was observed at this dose. At 1 200 mg/kg bw/day, a significant increase in clinical signs of toxicity was observed in dams, such as decreased food consumption, body weight gains, excess salivation, alopecia, ataxia, urine stained abdominal fur. Six of the 25 rats in the 1 200 mg/kg bw/day group died and necropsies showed that these rats had significantly increased adrenal weights. The authors assigned a developmental NOAEL of 50 mg/kg bw/day based on these results (US EPA 2006). In this assessment, the effects on fetuses and dams at 600 mg/kg bw/day were not considered sufficiently adverse. Adverse effects on fetal development were considered to occur only in the presence of maternal toxicity at 1200 mg/kg bw/day. Therefore, a NOAEL of 600 mg/kg bw/day has been defined.

Pine oil was generally negative for in vitro and in vivo genotoxicity (US EPA 2006), although one study found pine oil to be genotoxic to fruit flies and another showed an induction of chromosome aberrations in human lymphocytes (Lazutka et al. 2001). No chronic or carcinogenicity studies were identified for pine oil. Pine oil was reviewed in 2006 by the U.S. EPA, Office of Prevention, Pesticides and Toxic Substances in a Reregistration Eligibility Decision (RED) (US EPA 2006).

In order to further inform the risk assessment, the hazard information available for the main components of pine oil, alpha-terpineol (0-65%), alpha-pinene (12-69%), beta-pinene (0.17-33%), beta-myrcene (0-18%), camphene (0.8-11%), and limonene (0-16%), have been considered.

Hazard assessment of main components

Alpha-Terpineol

No classification of the health effects of alpha-terpineol by national or international regulatory agencies was identified.

Adverse effects were not observed in a developmental study that administered to male and female rats (10 animals/dose/sex) doses of 0, 60 or 250 mg/kg bw/day terpineol by gavage for 42 days (mating, pregnancy and lactation) with a 14-day recovery period to (ECHA 2018c). Based on the results of this study, the NOAEL for maternal and developmental effect was noticed to be up to 250 mg/kg bw/day by the authors of the study (ECHA 2018c).

Adverse effects were not observed in a repeated dose study that fed male and female rats (10 animals/dose/sex) 0, 1 000, 25 000 or 10 000 ppm (corresponding to 0, 100, 200 or 400 kg/kg bw/day) alpha-terpinyl acetate by diet for 20 weeks (ECHA 2018c). ECHA used read-across values from alpha-terpinyl acetate (structural analogue or surrogate) in order to define an oral NOAEL of 314 mg/kg bw/day with a correction for molecular weight for alpha-terpineol (ECHA 2018c).

Alpha-terpineol was not mutagenic in bacterial assays and did not induce gene mutations in mammalian cells either with or without exogenous metabolic activation (Belsito et al. 2008, Bhatia et al. 2008). In a 14-day repeated dose study in 3-4 male rats, administration of 1% alpha-terpineol supplemented ration caused a reduction in food intake, body weight and ApoA-1 (component of high density lipoprotein) levels. An increase in cholesterol, triacylglycerol levels and liver weight was also observed (Imaizumi et al. 1985).

Alpha-terpineol was evaluated for its potential to induce lung tumours in female A/He mice (Stoner et al. 1973). Mice were administered alpha-terpineol via intraperitoneal injection three times a week for 8 weeks for total cumulative doses of 1.9 and 9.6 g/kg (80 and 400 mg/kg bw/dose or 35 and 170 mg/kg bw/day). Mice were sacrificed 12 weeks following the last injection. At the 1.9 g/kg dose level, there were two deaths and tumours occurred in 3 of the 18 surviving animals. At the 9.6 g/kg dose level, there were five deaths and tumours occurred in 1 of the 15 surviving animals. There was no significant difference in tumour incidences between treated and control animals, and consequently, alpha-terpineol was determined to be not carcinogenic in this study.

Alpha- and Beta-Pinene

Alpha- and beta-pinene were reviewed by the US EPA in 2010 as a sponsored chemical (part of the Bicyclic Terpene Hydrocarbons category) under the HPV Challenge Program (US EPA 2009), which established a NOAEC of 50 ppm and LOAEC of 100 ppm. Further information on the health effects of alpha-pinene are provided in the Health effects assessment section for alpha-pinene (Section 8.3.2.2).

Beta-Myrcene

Beta-myrcene does not to pose a safety concern. Further information on the health effects of beta-myrcene are provided in the Health effects assessment section for lemongrass oil (Section 7.7.2.2).

Camphene

The US EPA has noticed a NOAEL of 250 mg/kg bw/day and a LOAEL of 1 000 mg/kg bw/day (US EPA 2010). Further information on the health effects of camphene are provided in the Health effects assessment section for turpentine/turpentine oil (Section 8.4.2.2).

Limonene

Limonene can be considered a substance of fairly low toxicity. Further information on the health effects of limonene are provided in the Potential to cause harm to human health section for sweet orange oil (Section 8.1.2).

8.6.2.3 Characterization of risk to human health

Oral:

The critical effect level identified for pine oil is a NOAEL of 600 mg/kg bw/day as identified in a rat developmental study. The effect level is based on maternal ataxia, impaired righting reflex, increased adrenal weights, and fetal deaths at the 1200 mg/kg bw/day dose level (Parent 1998 in US EPA 2006).

Dermal:

No effects were observed in the two dermal studies conducted with pine oil. However, one study only tested concentrations up to 226 mg/kg bw/day, while extremely limited information was provided in a review for the second study. In the absence of further information and in order to be conservative, the oral NOAEL of 600 mg/kg bw/day for pine oil as identified above was used for characterization of risk along with route-to-route extrapolation.

Inhalation:

No health effects data exists for pine oil via the inhalation route. Two options for points of departure for the inhalation route could be considered. Firstly, the oral NOAEL of 600 mg/kg bw/day as identified above could be used for quantification of risk along with route-to-route extrapolation. Absorption of pine oil via inhalation would be assumed to be equivalent to absorption via the oral route. Alternatively, the inhalation data for alpha-pinene, which comprises 12-69% of pine oil, could be used. However, as no critical health effects of concern were identified for the main component, alpha-terpeneol, which comprises 0-65% of pine oil, and there is good quality data for the parent oil, it was decided to use the oral NOAEL of 600 mg/kg bw/day for pine oil to characterize risk from the inhalation route of exposure to pine oil.

Table 8.6-2. Relevant exposure estimates, critical effect levels and resulting margins of exposure, for pine oil

Exposure Scenario[a]	**Systemic Exposure (mg/kg bw/day)**	**MOE[b]**
Food flavouring (dietary intake) - oral	2.97×10^{-4} (6 months and above)	2 020 202 (6 months and above)
Systemic exposure by the dermal and inhalation route from body lotion (0.3%)[c]	7.24×10^{-2} to 1.61×10^{-1} (adolescent-infant)	3 735 - 8 287 (infant–adolescent)
Systemic exposure by the dermal and inhalation routes from massage oil (1%)[d]	2.13×10^{-2} – 9.82×10^{-2} (adult–infant)	6 107 - 28 232 (infant–adult)

Exposure Scenario[a]	Systemic Exposure (mg/kg bw/day)	MOE[b]
Systemic exposure by the inhalation route from fragrance product (100%) (0.19 mg/m^3)	8.89 x 10^{-2} – 4.34 x 10^{-2} (adult–5 to 11 yrs)	6 749 - 13 825 (5 to 11 yrs–adult)
Systemic exposure by the dermal and inhalation route from mixing, loading, and application of an all-purpose floor cleaner (5%)	8.81 x 10^{-2} (adult)	6 810 (adult)
Systemic exposure by the dermal, inhalation, and non-dietary ingestion route from contacting cleaned floors (5%)	2.13 x 10^{-1} (toddler)	2 817 (toddler)
Systemic exposure by the inhalation route from automatic toilet bowl cleaner (10%) (0.29 mg/m^3)	6.63 x 10^{-2} – 1.74 x 10^{-1} (adult-toddler)	3 448 - 9 050 (toddler–adult)
Systemic exposure by the oral route from NMI in natural health products (0.4%)	2.82-3.37 mg/kg bw/day (adult-adolescent)	178 - 213 (adolescent–adult)

[a] Exposure scenario parameters and calculations for pine oil outlined in Appendix I.
[b] The margin of exposure was calculated using a critical effect level (NOAEL = 600 mg/kg bw/day) based on maternal effects of increased adrenal weights and death from an oral developmental toxicity study with pine oil.
[c] Assuming dermal absorption of 20% (occluded conditions).
[d] Assuming dermal absorption of 4% (unoccluded conditions).

The margins of exposure between the critical effect level and the estimate of exposure for scenarios listed in Table 8.6.2 are considered adequate to account for uncertainties in the health effects and exposure databases.

8.6.2.4 Uncertainties in evaluation of risk to human health

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

Table 8.6-3. Sources of uncertainty in the risk characterization for pine oil

Key source of Uncertainty	Impact
Exposure	
Combining both the dermal and inhalation routes for the cleaning scenarios, and the use of conservative assumptions to calculate exposure from each route of exposure, may result in conservative estimates.	+
Inhalation estimates for pine oil in products is very dependent upon factors such as room volume, ventilation rates, time spent in area of application and calculation of the time-weighted average. Each of these parameters has variability and uncertainty. Conservative assumptions were used.	+
There is a degree of uncertainty in extrapolating the dermal absorption data from linalool and citronellol to pine oil; however, as all the acyclic/monocyclic/bicyclic monoterpenes and constituents thereof have	+/-

Key source of Uncertainty	Impact
similar physical-chemical properties, the dermal absorption of these compounds is expected to be similar.	
Route-to-route extrapolation for pine oil was carried out for dermal scenarios in comparing to an effect level from an oral study.	+/-
Hazard	
There are no chronic or carcinogenicity animal studies for inhalation exposure.	+/-
There are no studies for dermal or inhalation exposure.	+/-
There are no or few animal studies examining the repeated-dose toxicity of pine oil for the relevant routes of exposure (i.e., dermal, oral, inhalation). Hazard data from the main components, alpha-terpineol and alpha-pinene, were used to inform the health effects assessment, where applicable.	+/-
The composition of the pine oil used in the rat developmental study is unknown. Therefore, it is unknown whether the composition of the pine oil used in the study is representative of the pine oil Canadians are exposed to.	+/-

+ = 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.

Conclusion

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 Acyclic, Monocyclic, and Bicyclic Monoterpenes Group. It is proposed to conclude that the 15 substances in the Acyclic, Monocyclic, and Bicyclic Monoterpenes Group do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that bois de rose oil, palmarosa oil, geranium oil, geranyllinalool, coriander oil, lemongrass oil, sweet orange oil, alpha-pinene, fir oil and pine oil 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.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that rose oil, mandarin oil, tangerine oil, turpentine oil and turpentine meet the criteria under paragraph 64(*c*) of CEPA as they are 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.

Therefore, it is proposed to conclude that rose oil, mandarin oil, tangerine oil, turpentine oil, and turpentine meet one or more of the criteria set out in section 64 of CEPA and that the remaining 10 substances in the Acyclic, Monocyclic, and Bicyclic Monoterpenes Group do not meet any of the criteria set out in section 64 of CEPA.

It is also proposed that rose oil, turpentine oil, and turpentine do not meet the persistence or bioaccumulation criteria, while mandarin and tangerine oil meet the bioaccumulation criteria but not the persistence criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

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Appendices

Appendix A. Exposure parameters used to estimate exposure to coriander oil

Table A-1. Exposure parameters for coriander oil body moisturizer (3%) scenario

Age Groups	Mean Product Amount (g/app)[a]	Mean Daily Frequency[b]	Air Conc. (mg/m^3) (24 hrs)[c]	Dermal Exposure (mg/kg bw/day)[d]	Inhalation Exposure (mg/kg bw/day)[e]	Combined Exposure (mg/kg bw/day)[f]
0-6 mths	2.5	0.8	1.40×10^{-2}	1.60	3.92×10^{-3}	1.60
6 mths-4 yrs	4.1	0.8	2.20×10^{-2}	1.27	1.32×10^{-2}	1.28
5-11 yrs	5	0.8	3.00×10^{-2}	7.74×10^{-1}	1.40×10^{-2}	7.88×10^{-1}
12-19 yrs	8.7	0.8	4.80×10^{-2}	7.03×10^{-1}	1.28×10^{-2}	7.16×10^{-1}
20+	10	1	5.50×10^{-2}	8.46×10^{-1}	1.26×10^{-2}	8.59×10^{-1}

[a] As cited in Ficheux et al. 2016

[b] As cited in Ficheux et al. 2015; Wu et al. 2010

[c] Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 80% of the applied dose was available for evaportation (amount remaining on skin surface following dermal absorption of the substance) (80%* product amount/applications * applications/day * 3% concentration), and using the following parameters: exposure duration of 24 hours, emission duration of 1 hour, room volume of 80 m^3, ventilation rate of 1/hr, surface area equal to exposed skin (assumed equal to head, arms and hands) (1365 cm^2 for 0-6 mths, 1970 cm^2 for 6 mths-4 yrs, 2900 cm^2 for 5-11 yrs, 4540 cm^2 for 12-19 yrs, and 4735 cm^2 for adults as cited in Health Canada 1998), molelcular weight matrix of 125 g/mol, and application temperature of 37°C.

[d] Dermal exposure calculated using the following formula: [mean product (g/application)*mean daily frequency (applications/day)* product concentration (3%) * dermal absorption for occluded skin (20%)*conversion factor (1000 mg/g)] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998)

[e] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) *Inhalation rate (m^3/day) (2.1 m^3/day for 0-6 mths, 9.3 m^3/day for 6 mths-4 yrs, 14.5 m^3/day for 5-11 yrs, 15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).

[f] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)

Table A-2. Exposure parameters for coriander oil massage oil scenario

Age Groups	Mean product amount (g/day)[a]	Air Concentration (24 hrs) (mg/m^3)[b]	Dermal Exposure (mg/kg bw/day)[c]	Inhalation Exposure (mg/kg bw/day)[d]	Combined Exposure (mg/kg bw/day)[e]
0-6 mths	2.60×10^{-2}	1.20×10^{-2}	1.39×10^{-1}	3.36×10^{-3}	1.42×10^{-1}
6 mths-4 yrs	2.60×10^{-2}	1.20×10^{-2}	6.72×10^{-2}	7.20×10^{-3}	7.44×10^{-2}

Age Groups	Mean product amount (g/day)[a]	Air Concentration (24 hrs) (mg/m^3)[b]	Dermal Exposure (mg/kg bw/day)[c]	Inhalation Exposure (mg/kg bw/day)[d]	Combined Exposure (mg/kg bw/day)[e]
5 to 11 yrs	2.60×10^{-2}	1.20×10^{-2}	3.36×10^{-2}	5.61×10^{-3}	3.92×10^{-2}
12 to 19 yrs	2.60×10^{-2}	1.20×10^{-2}	1.75×10^{-2}	3.19×10^{-3}	2.07×10^{-2}
20+	2.60×10^{-2}	1.10×10^{-2}	1.47×10^{-2}	2.51×10^{-3}	1.72×10^{-2}

[a] Calculated from 2 drops of oil (label directions) = 0.1mL from 30% upper concentration then multiplied by coriander oil density of 0.868 g/mL => 0.1 x 0.3 x 0.868. Assumed frequency of 1 massage per day.

[b] Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 96% of the applied dose was available for evaporation (amount remaining on skin surface following dermal absorption of the substance) (96%* product amount/day), and using the following parameters: exposure duration of 24 hours, emission duration of 1 hour, room volume of 80 m^3, ventilation rate of 1/hr, release area equal to exposed surface area (total surface area minus head for 0-11 years and total surface area minus one-half head and trunk for adults and adolescents) (3020 cm^2 for 0-6 mths, 4910 cm^2 for 6 mths-4 yrs, 8450 cm^2 for 5-11 yrs, 12795 cm^2 for 12-19 yrs, and 14380 cm^2 for 20+ yrs as cited in Health Canada 1998), molelcular weight matrix of 125 g/mol, and application temperature of 37°C.

[c] Dermal exposure calculated using the following formula: [mean product (g/day) *dermal absorption for unoccluded skin (4%)*conversion factor (1000 mg/g)] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998)

[d] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) * Inhalation rate (m^3/day) (2.1 m^3/day for 0-6 mths, 9.3 m^3/day for 6 mths-4 yrs, 14.5 m^3/day for 5-11 yrs, 15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).

[e] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)

Table A-3. Inhalation exposure parameters for coriander oil perfume scenario (instantaneous release)

Age Groups	Mean Product Amount (g/app)[a]	Mean Daily Frequency[a]	Product Concentration (%)	Air Concentration (mg/m^3) (24hr)[c]	Exposure (mg/kg bw/day)[c]
5 to 11 years	0.33	1.7	10	0.019	8.89×10^{-3}
12 to 19 years	0.33	1.7	10	0.019	5.05×10^{-3}
20+	0.33	1.7	10	0.019	4.34×10^{-3}

[a] As cited in Loretz et al. 2005

[b] ConsExpo parameters used= exposure duration of 5 min, room volume of 10m^3 (bathroom), 0 per hour ventilation rate

[c] Internal dose (mg/kg bw/day)= ([mean mg/m^3] x inhalation rate (14.5 m^3/day for 5-11 yrs; 15.8 m^3/day for 12-19 yrs; 16.2 m^3/day for 20^+))/body weight (31 kg for 5-11 yrs; 59.4 kg for 12-19 yrs; 70.9 kg for 20+). Inhalation rates and body weights as cited in HC 1998.

Appendix B. Exposure parameters used to estimate exposure to rose oil

Table B-1a. Exposure parameters for rose oil body moisturizer scenario (3%)

Age Groups	Mean Product Amount (g/app)[a]	Mean Daily Frequency[b]	Air Conc. (mg/m^3) (24 hrs)[c]	Dermal Exposure (mg/kg bw/day)[d]	Inhalation Exposure (mg/kg bw/day)[e]	Combined Exposure (mg/kg bw/day)[f]
0-6 mths	2.5	0.8	5.40×10^{-3}	1.60	1.51×10^{-3}	1.60
6 mths-4 yrs	4.1	0.8	7.80×10^{-3}	1.27	4.68×10^{-3}	1.27
5-11 yrs	5	0.8	1.10×10^{-2}	7.74×10^{-1}	5.15×10^{-3}	7.79×10^{-1}
12-19 yrs	8.7	0.8	1.80×10^{-2}	7.03×10^{-1}	4.79×10^{-3}	7.08×10^{-1}
20+	10	1	1.90×10^{-2}	8.46×10^{-1}	4.34×10^{-3}	8.51×10^{-1}

[a] As cited in Ficheux et al. 2016

[b] As cited in Ficheux et al. 2015; Wu et al. 2010

[c] Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 80% of the applied dose was available for evaporation (amount remaining on the skin surface following dermal absorption of the substance) (80%* product amount/applications * applications/day * 3% concentration), and using the following parameters: exposure duration of 24 hours, emission duration of 1 hour, room volume of 80 m^3, ventilation rate of 1/hr, surface area equal to exposed skin (assumed equal to head, arms and hands) (1365 cm^2 for 0-6 mths, 1970 cm^2 for 6 mths-4 yrs, 2900 cm^2 for 5-11 yrs, 4540 cm^2 for 12-19 yrs, and 4735 cm^2 for adults as cited in Health Canada 1998), molelcular weight matrix of 125 g/mol, and application temperature of 37°C.

[d] Dermal exposure calculated using the following formula: [mean product (g/application)*mean daily frequency (applications/day)* product concentration (3%) * dermal absorption for occluded skin (20%)*conversion factor (1000 mg/g)] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998)

[e] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) *Inhalation rate (m^3/day) (2.1 m^3/day for 0-6 mths, 9.3 m^3/day for 6 mths-4 yrs, 14.5 m^3/day for 5-11 yrs, 15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).

[f] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)

Table B-1b. Exposure parameters for rose oil body moisturizer scenario (1%)

Age Groups	Mean Product Amount (g/app)[a]	Mean Daily Frequency[b]	Air Conc. (mg/m^3) (24 hrs)[c]	Dermal Exposure (mg/kg bw/day)[d]	Inhalation Exposure (mg/kg bw/day)[e]	Combined Exposure (mg/kg bw/day)[f]
0-6 mths	2.5	0.8	1.80×10^{-3}	5.33×10^{-1}	5.04×10^{-3}	5.34×10^{-1}
6 mths-4 yrs	4.1	0.8	2.60×10^{-3}	4.23×10^{-1}	1.56×10^{-3}	4.25×10^{-1}
5-11 yrs	5	0.8	3.70×10^{-3}	2.58×10^{-1}	1.73×10^{-3}	2.60×10^{-1}
12-19 yrs	8.7	0.8	5.80×10^{-3}	2.34×10^{-1}	1.54×10^{-3}	2.36×10^{-1}
20+	10	1	6.30×10^{-3}	2.82×10^{-1}	1.44×10^{-3}	2.84×10^{-1}

[a] As cited in Ficheux et al. 2016
[b] As cited in Ficheux et al. 2015; Wu et al. 2010
[c] Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 80% of the applied dose was available for evaporation (amount remaining on the skin surface following dermal absorption of the substance) (80%* product amount/applications * applications/day * 1% concentration), and using the following parameters: exposure duration of 24 hours, emission duration of 1 hour, room volume of 80 m^3, ventilation rate of 1/hr, surface area equal to exposed skin (assumed equal to head, arms and hands) (1365 cm^2 for 0-6 mths, 1970 cm^2 for 6 mths-4 yrs, 2900 cm^2 for 5-11 yrs, 4540 cm^2 for 12-19 yrs, and 4735 cm^2 for adults as cited in Health Canada 1998), molelcular weight matrix of 125 g/mol, and application temperature of 37°C.
[d] Dermal exposure calculated using the following formula: [mean product (g/application)*mean daily frequency (applications/day)* product concentration (1%) * dermal absorption for occluded skin (20%)*conversion factor (1000 mg/g)] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998)
[e] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) *Inhalation rate (m^3/day) (2.1 m^3/day for 0-6 mths, 9.3 m^3/day for 6 mths-4 yrs, 14.5 m^3/day for 5-11 yrs, 15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).
[f] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)

Table B-2. Exposure parameters for rose oil massage oil scenario

Age Groups	Mean product amount (g/day)[a]	Air Concentration (24 hrs) (mg/m^3)[b]	Dermal Exposure (mg/kg bw/day)[c]	Inhalation Exposure (mg/kg bw/day)[d]	Combined Exposure (mg/kg bw/day)[e]
0-6 mths	6.84×10^{-2}	3.10×10^{-2}	3.65×10^{-1}	8.68×10^{-3}	3.74×10^{-1}
6 mths-4 yrs	6.84×10^{-2}	3.10×10^{-2}	1.77×10^{-1}	1.86×10^{-2}	1.95×10^{-1}
5 to 11 yrs	6.84×10^{-2}	3.00×10^{-2}	8.83×10^{-2}	1.40×10^{-2}	1.02×10^{-1}
12 to 19 yrs	6.84×10^{-2}	3.00×10^{-2}	4.61×10^{-2}	7.98×10^{-3}	5.40×10^{-2}
20+	6.84×10^{-2}	3.00×10^{-2}	3.86×10^{-2}	6.85×10^{-3}	4.55×10^{-2}

[a] Calculated from 5 drops of oil (label directions) = 0.25 mL (each drop equals 0.05 mL) from 30% upper concentration then multiplied by rose oil density of 0.9125 g/mL = 0.25 x 0.3 x 0.9125. Assumed frequency of 1 massage per day.
[b] Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 96% of the applied dose was available for evaporation (amount remaining on the skin surface following dermal absorption of the substance) (96%* product amount/day), and using the following parameters: exposure duration of 24 hours, emission duration of 1 hour, room volume of 80 m^3, ventilation rate of 1/hr, release area equal to exposed surface area (total surface area minus head for 0-11 years and total surface area minus one-half head and trunk for adults and adolescents) (3020 cm^2 for 0-6 mths, 4910 cm^2 for 6 mths-4 yrs, 8450 cm^2 for 5-11 yrs, 12795 cm^2 for 12-19 yrs, and 14380 cm^2 for 20+ yrs as cited in Health Canada 1998), molelcular weight matrix of 125 g/mol, and application temperature of 37°C.
[c] Dermal exposure calculated using the following formula: [mean product (g/day) *dermal absorption for unoccluded skin (4%)*conversion factor (1000 mg/g)] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998)
[d] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) * Inhalation rate (m^3/day) (2.1 m^3/day for 0-6 mths, 9.3 m^3/day for 6 mths-4 yrs, 14.5 m^3/day for 5-11 yrs, 15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).
[e] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)

Table B-3. Exposure parameters for rose oil face moisturizer scenario (3%)

Age Groups*	Mean Product Amount (g/event) [a]	Mean Events per Day[a]	Air Conc. (mg/m^3) (24 hrs)[c]	Dermal Exposure (mg/kg bw/day)[c]	Inhalation Exposure (mg/kg bw/day)[d]	Combined Exposure (mg/kg bw/day)[e]
12 to 19 yrs	1.0	1.5	9.90×10^{-2}	3.03×10^{-2}	2.63×10^{-2}	5.66×10^{-2}
20+	2.0	1.5	9.20×10^{-2}	5.08×10^{-2}	2.10×10^{-2}	7.18×10^{-2}

* Only two age groups are appliable for the face moisturizer scenario

[a] As cited in Loretz et al. 2005; Ficheux et al. 2015 & 2016

[b] Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 96% of the applied dose was available for evaporation (amount remaining on the skin surface following dermal absorption of the substance) (96%* product amount/applications * applications/day * 3% concentration), and using the following parameters: exposure duration of 24 hours, emission duration of 1 hour, room volume of 1 m^3 (approximate personal breathing zone), release area equal to surface area of application (assumed equivalent to one-half of head (730 cm^2 for 12-19 yrs, and 637.5 cm^2 for adults as cited in Health Canada 1998), ventilation rate of 2/hr (approximate mixing of air between personal breathing zone and the room), molelcular weight matrix of 125 g/mol, and application temperature of 37°C.

[c] Dermal exposure calculated using the following formula: [mean product (g/application)*mean daily frequency (applications/day)*product concentration (3%)*dermal absorption for unoccluded skin (4%)*conversion factor (1000 mg/g)] ÷ body weight (59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998)

[c] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) * Inhalation rate (m^3/day) (15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).

[d] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)

Table B-4. Inhalation exposure parameters for rose oil perfume scenario (instantaneous release)

Age Groups	Mean Product Amount (g/app)[a]	Mean Daily Frequency[a]	Product Concentration (%)	Air Concentration (mg/m^3) (24hr)[b]	Exposure (mg/kg bw/day)[c]
5 to 11 yrs	0.33	1.7	100	0.19	8.89×10^{-2}
12 to 19 yrs	0.33	1.7	100	0.19	5.05×10^{-2}
20+	0.33	1.7	100	0.19	4.34×10^{-2}

[a] As cited in Loretz et al. 2005

[b] ConsExpo parameters used= exposure duration of 5 min, room volume of 10m^3 (bathroom), 0 per hour ventilation rate

[c] Internal dose (mg/kg bw/day)= ([mean mg/m^3] x inhalation rate (14.5 m^3/day for 5-11 yrs; 15.8 m^3/day for 12-19 yrs; 16.2 m^3/day for 20^+))/body weight (31 kg for 5-11 yrs; 59.4 kg for 12-19 yrs; 70.9 kg for 20+). Inhalation rates and body weights as cited in HC 1998.

Appendix C. Exposure parameters used to estimate exposure to lemongrass oil

Table C-1. Exposure parameters for lemongrass oil body moisturizer (5%) scenario

Age Groups	Mean Product Amount (g/app)[a]	Mean Daily Frequency[b]	Air Conc. (mg/m^3) (24 hrs)[c]	Dermal Exposure (mg/kg bw/day)[d]	Inhalation Exposure (mg/kg bw/day)[e]	Combined Exposure (mg/kg bw/day)[f]
0-6 mths	2.5	0.8	1.6×10^{-2}	2.67	4.49×10^{-3}	2.67
6 mths-4 yrs	4.1	0.8	2.4×10^{-2}	2.12	1.44×10^{-2}	2.13
5-11 yrs	5	0.8	3.4×10^{-2}	1.29	1.59×10^{-2}	1.31
12-19 yrs	8.7	0.8	5.4×10^{-2}	1.17	1.44×10^{-2}	1.19
20+	10	1	5.9×10^{-2}	1.41	1.35×10^{-2}	1.42

[a] As cited in Ficheux et al. 2016

[b] As cited in Ficheux et al. 2015; Wu et al. 2010

[c] Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 80% of the applied dose was available for evaporation (amount remaining on the skin surface following dermal absorption of the substance) (80%* product amount/applications * applications/day * 5% concentration), and using the following parameters: exposure duration of 24 hours, emission duration of 1 hour, room volume of 80 m^3, ventilation rate of 1/hr, surface area equal to exposed skin (assumed equal to head, arms and hands) (1365 cm^2 for 0-6 mths, 1970 cm^2 for 6 mths-4 yrs, 2900 cm^2 for 5-11 yrs, 4540 cm^2 for 12-19 yrs, and 4735 cm^2 for adults as cited in Health Canada 1998), molelcular weight matrix of 125 g/mol, and application temperature of 37°C.

[d] Dermal exposure calculated using the following formula: [mean product (g/application)*mean daily frequency (applications/day)* product concentration (5%) * dermal absorption for occluded skin (20%)*conversion factor (1000 mg/g)] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998)

[e] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) *Inhalation rate (m^3/day) (2.1 m^3/day for 0-6 mths, 9.3 m^3/day for 6 mths-4 yrs, 14.5 m^3/day for 5-11 yrs, 15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).

[f] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)

Table C-2. Exposure parameters for lemongrass oil massage oil scenario

Age Groups	Mean product amount (g/day)[a]	Air Concentration (24 hrs) (mg/m^3)[b]	Dermal Exposure (mg/kg bw/day)[c]	Inhalation Exposure (mg/kg bw/day)[d]	Combined Exposure (mg/kg bw/day)[e]
0-6 mths	1.80×10^{-1}	8.20×10^{-2}	9.59×10^{-1}	2.30×10^{-2}	9.82×10^{-1}
6 mths-4 yrs	1.80×10^{-1}	8.10×10^{-2}	4.64×10^{-1}	4.86×10^{-2}	5.13×10^{-1}
5 to 11 yrs	1.80×10^{-1}	8.00×10^{-2}	2.32×10^{-1}	3.74×10^{-2}	2.69×10^{-1}
12 to 19 yrs	1.80×10^{-1}	8.00×10^{-2}	1.21×10^{-1}	2.13×10^{-2}	1.42×10^{-1}
20+	1.80×10^{-1}	8.00×10^{-2}	1.01×10^{-1}	1.83×10^{-2}	1.20×10^{-1}

[a] Calculated from 4 drops of oil 0.2 mL (assume each drop is equivalent to 0.05 mL) from 100% upper concentration (it was the only notified ingredient) then multiplied by lemongrass oil density of 0.899 g/mL => 0.2 x 1 x 0.899. Assumed frequency of 1 massage per day.

[b] Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 96% of the applied dose was available for evaporation (amount remaining on the skin surface following dermal absorption of the substance) (96%* product amount/day), and using the following parameters: exposure

duration of 24 hours, emission duration of 1 hour, room volume of 80 m^3, ventilation rate of 1/hr, release area equal to exposed surface area (total surface area minus head for 0-11 years and total surface area minus one-half head and trunk for adults and adolescents) (3020 cm^2 for 0-6 mths, 4910 cm^2 for 6 mths-4 yrs, 8450 cm^2 for 5-11 yrs, 12795 cm^2 for 12-19 yrs, and 14380 cm^2 for 20+ yrs as cited in Health Canada 1998), molelcular weight matrix of 125 g/mol, and application temperature of 37°C.

[c] Dermal exposure calculated using the following formula: [mean product (g/day) *dermal absorption for unoccluded skin (4%)*conversion factor (1000 mg/g)] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998)

[d] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) * Inhalation rate (m^3/day) (2.1 m^3/day for 0-6 mths, 9.3 m^3/day for 6 mths-4 yrs, 14.5 m^3/day for 5-11 yrs, 15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).

[e] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)

Table C-3. Inhalation exposure parameters for lemongrass oil perfume scenario (instantaneous release)

Age Groups	Mean Product Amount (g/app)[a]	Mean Daily Frequency[a]	Product Concentration (%)	Air Concentration (mg/m^3)[b] (24hr)
5 to 11 years	0.33	1.7	30	0.058
12 to 19 years	0.33	1.7	30	0.058
20+	0.33	1.7	30	0.058

[a] Loretz et al. 2005

[b] ConsExpo parameters used= exposure duration of 5 min, room volume of 10m^3 (bathroom), 0 per hour ventilation rate

Table C-4. Other exposure scenarios for lemongrass oil (dermal, inhalation, oral)

Exposure Scenario	Age Group	Concentration	Dermal Intake (µg/kg bw/day)	Inhalation Exposure (µg/m^3)	Oral Intake (µg/kg bw/day)
Mixing, loading, and application of an all-purpose floor cleaner	Adult	1%	2.08	1.90	N/A
Exposure from contacting cleaned floors	Toddler	1%	1.29	1.90	3.22

*****Details on the method and parameters used to estimate inhalation and dermal exposure to lemongrass oil from products that are available to consumers are provided in Table C-6.

Table C-5: Exposure parameter assumptions for lemongrass oil

Exposure Scenario	Assumptions*
Mixing, loading and application of an all-purpose floor cleaner (liquid) (adult)	Concentration of lemongrass oil: 1% (assumed maximum concentration when lemongrass oil is used as a fragrance in cleaners). Mixing and loading (dermal): Product amount: 0.01 g Dermal absorption: 4% (unoccluded skin) Mixing and loading (inhalation: exposure to vapour-evaporation-constant release area model) Exposure duration: 0.75 min Product amount: 500 g Room volume: 1 m^3 Ventilation rate: 0.5 per hour Release area: 20 cm^2 Emission duration: 0.3 min Application temperature: 20°C Mass transfer coefficient: 10 m/h Molecular weight matrix: 36 g/mol Application (dermal): Product amount: 0.36 g Dermal absorption: 4% (unoccluded skin) Application (inhalation: exposure to vapour-evaporation-increasing release model): Exposure duration: 240 min Amount of solution used: 900 g Dilution (times): 62 Room volume: 58 m^3 Ventilation rate: 0.5 per hour Release area: 22 m^2 Application duration: 20 min Application temperature: 20°C Mass transfer coefficient: 10 m/h Molecular weight matrix: 18 g/mol Combined exposure: total dermal (mixing/loading + application) + total inhalation (mixing/loading + application)
Exposure from contacting cleaned floors (toddler)	Concentration of lemongrass oil: 1% (assumed maximum concentration when lemongrass oil is used as a fragrance in cleaners). Calculations based on the US EPA Residential SOPs (2012), Section 7. Dermal: Calculated using the following algorithm:

Exposure Scenario	Assumptions*
	Exposure (mg/kg bw/day) = [deposited residue (mg/cm^2) * fraction available for transfer (%) * transfer coefficient (cm^2/hr) * exposure time (hrs) * dermal absorption (%)]/body weight Deposited residue (µg/cm^2): Calculated assuming 14.4 g of product per 22 m^2 of floor (ConsExpo Cleaning Fact Sheet, 2018) * 1000 mg/g * 1 m^2/10000 cm^2 Transfer coefficient: 2200 cm^2/hr (adjusted for the surface area of a toddler aged 6 months to 4 years using the following formula; adult transfer coefficient 6800 cm^2/hr * (5780 cm^2 surface area toddler/18200 cm^2 surface area adult)) Fraction available for transfer: 8% Exposure time: 2 hr; exposure time for hard surfaces represents time spent in kitchens and bathrooms Dermal absorption: 4% (unoccluded skin) Incidental Oral (i.e. hand-to-mouth exposure): Calculated using the following algorithm: Exposure (mg/day) = [HR (mg/cm^2) * (F_M * SA_H (cm^2)) * (ET * N_Replen) * (1 – (1 – SE)$^{Freq\_HtM/N\_Replen}$)] HR: hand residue loading (mg/cm^2); calculated using the following algorithm: HR = [Fai_{hands} * Dermal exposure (mg) (calculated above)] / (SA_H * 2) Fai_{hands}: 0.15 (unitless); fraction of active ingredient on hands compared to total surface residue from jazzercise study SA_H: 150 cm^2; typical surface area of one hand F_M: 0.13 (unitless); fraction of hand mouthed per event SA_H: 150 cm^2; typical surface area of one hand ET: 2 hours; exposure time per day N_Replen: 4; number of replenishment intervals per hour SE: 0.48; saliva extraction factor Freq_HtM: 20; number of hand-to-mouth events per hour Inhalation: Air concentration from application of liquid floor cleaner (see above for parameters) Combined exposure: dermal + oral + inhalation

*Exposure to products was estimated using ConsExpo Web (2016). Exposure estimates were calculated based on default body weights and inhalation rates of 70.9 kg/16.2 m^3/day, 59.4 kg/15.8 m^3/day, 31 kg/14.5 m^3/day, 15.5 kg/9.3 m^3/day, and 7.5 kg/2.1 m^3/day for adults, (20 years and older), adolescents (12 to 19 years old), children (5 to 11 years old), toddlers (6 months to 4 years old), and infants (0 to 6 months old), respectively (HC 1998). Unless specified, the defaults come from the relevant ConsExpo Fact Sheet for the scenario presented.

Appendix D. Exposure parameters used to estimate worst case exposures to aromatherapy

Table D-1. Aromatherapy scenario parameters adapted

Worst case parameters used to calculate average concentration	Reference; Danish EPA 2008
Quantity of oil	10 drops = 0.4 g
Volume of room	17.4 m^3 (small room)
Time the lamp is used	2 hrs
Time of exposure at use cycle	4 hrs
Air exchange rate	50% per hr
Diffuser type	Aroma lamps
Average concentration in 4 hrs	1.45 mg/m^3

Table D-2. Aromatherapy (diffuser) scenario for rose oil, coriander oil, and mandarin/tangerine oils

Age Groups*	Room Air Concentration (mg/m^3) (4 hrs)[a]	Average Air Concentration (mg/m^3) (24hrs)[b]	Exposure (mg/kg bw/day)[c]	Adjusted Exposure mandarin/tangerine (mg/kg bw/day)[d,e]
0-6 months	1.45	0.24	6.77×10^{-2}	NA
6 months-4 years	1.45	0.24	1.45×10^{-1}	NA
5 to 11 years	1.45	0.24	1.13×10^{-1}	NA
12 to 19 years	1.45	0.24	6.43×10^{-2}	3.86×10^{-2}
20+	1.45	0.24	5.52×10^{-2}	3.33×10^{-2}

* Standard Health Canada inhalation rates and body weight (HC 1998) were used in this calculation.

[a] All parameters listed in Table D-1

[b] Calculated using the following formula: (Air concentation (1.45 mg/m^3) * 4 hours)/ 24 hours

[c] Exposure dose = (average concentration in room (24 hrs) x daily inhalation rate)/ body weight

[d] Adjusted exposure dose by 60% to account for the maximum amount of gamma-terpinene in mandarin/tangerine oil (61% in leaf, Lota et al. 2000).

Table D-3. Aromatherapy (diffuser) scenario for lemongrass oil and alpha-pinene

Aromatherapy Inhalation Scenario (lemongrass oil)	Exposure Ave. concentration in room (mg/m^3) (4 hours)*
No specific age group	1.45

* Parameter listed in Table D-1

Appendix E. Exposure parameters used to estimate exposure to mandarin/tangerine oil

Table E-1. Exposure parameters for mandarin/tangerine oil body moisturizer (5%) scenario

Age Groups	Mean Product Amount (g/app)[a]	Mean Daily Frequency[b]	Dermal Exposure (mg/kg bw/day)[c]	Inhalation Exposure (mg/kg bw/day)[d]	Combined Exposure (mg/kg bw/day)[e]	Adjusted Combined Exposure (mg/kg bw/day)[f]
12 to 19 years	8.7	0.8	1.17	3.72×10^{-2}	1.21	7.25×10^{-1}
20+	10	1	1.41	4.57×10^{-2}	1.46	8.74×10^{-1}

[a] As cited in Ficheux et al. 2016
[b] As cited in Ficheux et al. 2015; Wu et al. 2010
[c] Dermal exposure calculated using the following formula: [mean product (g/application)*mean daily frequency (applications/day)* product concentration (5%) * dermal absorption for occluded skin (20%)*conversion factor (1000 mg/g)] ÷ body weight (59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).
[d] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) * Inhalation rate (m^3/day) (15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998). Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 80% of the applied dose was available for evaporation (amount remaining on the skin surface following dermal absorption of the substance) (80%* product amount/applications * applications/day * 5% concentration), and using the following parameters: exposure duration of 24 hours, emission duration of 1 hour, room volume of 80 m^3, ventilation rate of 1/hr, surface area equal to exposed skin (assumed equal to head, arms and hands) (1365 cm^2 for 0-6 mths, 1970 cm^2 for 6 mths-4 yrs, 2900 cm^2 for 5-11 yrs, 4540 cm^2 for 12-19 yrs, and 4735 cm^2 for adults as cited in Health Canada 1998), molelcular weight matrix of 125 g/mol, and application temperature of 37°C. Air concentrations ranged from 0.14-0.20 mg/m^3.
[e] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day).
[f] Adjusted exposure dose by 60% to account for the maximum amount of gamma-terpinene in mandarin/tangerine oil (61% in leaf, Lota et al. 2000).

Table E-2. Dermal exposure parameters for mandarin/tangerine oil sunscreen scenario

Age Groups	Mean Product Amount (g/day)[a]	Mean Daily Frequency	Product Concentration (%)	Body Weight (kg)[b]	Exposure (mg/kg bw/day)[c]	Adjusted Exposure (mg/kg bw/day)[d]
12 to 19 years	18.2	1.4	1	59.4	1.72×10^{-1}	1.03×10^{-1}
20+	18.2	1.6	1	70.9	1.44×10^{-1}	8.63×10^{-2}

[a] Based on chronic exposure using data from Ficheux et al., 2015, 2016.
[b] As cited in Health Canada 1988
[c] Assuming dermal absorption of 4% (unoccluded skin)
[d] Adjusted exposure dose by 60% to account for the maximum amount of gamma-terpinene in mandarin/tangerine oil (61% in leaf, Lota et al. 2000).

Table E-3. Inhalation exposure parameters for mandarin/tangerine oil perfume scenario (instantaneous release) (30%)

Age Groups	Mean product amount (g/app)[a]	Mean Daily Frequency[a]	Air Concentration (mg/m^3)[b] (24hr)	Exposure (mg/kg bw/day)[c]	Adjusted Exposure (mg/kg bw/day)[d]
12 to 19 years	0.33	1.7	0.058	1.54×10^{-2}	9.26×10^{-3}
20+	0.33	1.7	0.058	1.33×10^{-2}	7.95×10^{-3}

[a] As cited in Loretz et al. 2005
[b] ConsExpo parameters used= exposure duration of 5 min, room volume of $10m^3$ (bathroom), 0 per hour ventilation rate
[c] Internal dose (mg/kg bw/day)= ([mean mg/m^3] x inhalation rate (15.8 m^3/day for 12-19 yrs; 16.2 m^3/day for 20^+))/body weight (59.4 kg for 12-19 yrs; 70.9 kg for 20+). Inhalation rates and body weights as cited in HC 1998.
[d] Adjusted exposure dose by 60% to account for the maximum amount of gamma-terpinene in mandarin/tangerine oil (61% in leaf, Lota et al. 2000).

Table E-4. Dermal exposure parameters for mandarin/tangerine oil massage oil scenario

Age Groups	Mean product amount (g/day)[a]	Air Conc. (24 hrs) (mg/m^3)[b]	Dermal Exposure (mg/kg bw/day)[c]	Inhalation Exposure (mg/kg bw/day)[d]	Combined Exposure (mg/kg bw/day)[e]	Adjusted Combined Exposure (mg/kg bw/day)[f]
12-19 yrs	1.68×10^{-1}	7.50×10^{-2}	1.13×10^{-1}	1.99×10^{-2}	1.33×10^{-1}	8.00×10^{-2}
20+	1.68×10^{-1}	7.40×10^{-2}	9.50×10^{-2}	1.69×10^{-2}	1.12×10^{-1}	6.71×10^{-2}

[a] Calculated from 4 drops of oil, which is 0.2 mL (one drop is equivalent to 0.05 mL) from 100% upper concentration then multiplied by mandarin/tangerine oil density of 0.842 g/mL => 0.2 x 1 x 0.842. Assumed frequency of 1 massage per day.
[b] Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 96% of the applied dose was available for evaporation (amount remaining on the skin surface following dermal absorption of the substance) (96%* product amount/day), and using the following parameters: exposure duration of 24 hours, emission duration of 1 hour, room volume of 80 m^3, ventilation rate of 1/hr, release area equal to exposed surface area (total surface area minus head for 0-11 years and total surface area minus one-half head and trunk for adults and adolescents) (3020 cm^2 for 0-6 mths, 4910 cm^2 for 6 mths-4 yrs, 8450 cm^2 for 5-11 yrs, 12795 cm^2 for 12-19 yrs, and 14380 cm^2 for 20+ yrs as cited in Health Canada 1998), molelcular weight matrix of 125 g/mol, and application temperature of 37°C.
[c] Dermal exposure calculated using the following formula: [mean product (g/day) *dermal absorption for unoccluded skin (4%)*conversion factor (1000 mg/g)] ÷ body weight (59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998)
[d] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) * Inhalation rate (m^3/day) (15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).
[e] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)
[f] Adjusted exposure dose by 60% to account for the maximum amount of gamma-terpinene in mandarin/tangerine oil (61% in leaf, Lota et al. 2000).

Table E-5. Other exposure scenarios for mandarin/tangerine oil (dermal, inhalation, oral)

Exposure Scenario[a]	Age Group	Concentration or Amount	Dermal Intake (µg/kg bw/day)[b]	Inhalation Exposure (µg/kg bw/day)[b]	Oral Intake (µg/kg bw/day)[b]
Mixing, loading, and application of a liquid all-purpose floor cleaner	Adult	1%	1.25 (2.09)	3.70 (6.17) (27.0 µg/m^3 – 24 hrs)	N/A
Mixing, loading, and hanging machine-washed laundry	Adult	5%	9.09 (15.1)	1.02 (1.69) (7.40 µg/m^3 – 24 hrs)	N/A
Non-medicinal ingredient in dietary supplements	Adult	3.53%	N/A	N/A	254 (423)

[a] Details on the method and parameters used to estimate inhalation and dermal exposure mandarin oil from products that are available to consumers are provided in Table E-6.

[b] Exposure dose adjusted by 60% to account for the maximum amount of gamma-terpinene in mandarin/tangerine oil (61% in leaf, Lota et al. 2000). Dose in brackets is the non-adjusted dose.

Table E-6: Exposure parameter assumptions for mandarin/tangerine oil

Exposure Scenario	Assumptions*
Mixing, loading and application of an all-purpose floor cleaner (liquid) (adult)	Concentration of mandarin oil: 1% (assumed maximum concentration when mandarin/tangerine oil is used as a fragrance in cleaners based on ACI (2018)). Mixing and loading (dermal): Product amount: 0.01 g Dermal absorption: 4% (unoccluded skin) Mixing and loading (inhalation: exposure to vapour-evaporation-constant release area model) Exposure duration: 0.75 min Product amount: 500 g Room volume: 1 m^3 Ventilation rate: 0.5 per hour Release area: 20 cm^2 Emission duration: 0.3 min Application temperature: 20°C Mass transfer coefficient: 10 m/h Molecular weight matrix: 36 g/mol Application (dermal): Product amount: 0.36 g Dermal absorption: 4% (unoccluded skin)

Exposure Scenario	Assumptions*
	Application (inhalation: exposure to vapour-evaporation-increasing release model): Exposure duration: 240 min Amount of solution used: 900 g Dilution (times): 62 Room volume: 58 m^3 Ventilation rate: 0.5 per hour Release area: 22 m^2 Application duration: 20 min Application temperature: 20°C Mass transfer coefficient: 10 m/h Molecular weight matrix: 18 g/mol Combined exposure: total dermal (mixing/loading + application) + total inhalation (mixing/loading + application) * 60% (adjustment based on the maximum amount of gamma-terpinene in mandarin/tangerine oil)
Mixing and loading (liquid) and hanging machine-washed clothing (adult)	Concentration of mandarin oil: 5% (assumed maximum concentration when mandarin oil is used as a fragrance in liquid detergent for laundry machines based on ACI (2018)). Mixing and loading (dermal): Product amount: 0.53 g Dermal absorption: 4% (unoccluded skin) Mixing and loading (inhalation: exposure to vapour-evaporation-constant release area): Exposure duration: 0.75 min Product amount: 500 g Room volume: 1 m^3 Ventilation rate: 0.6 per hour Release area: 20 cm^2 Emission duration: 0.3 min Application temperature: 20°C Mass transfer coefficient: 10 m/h Molecular weight matrix: 90 g/mol Hanging machine-washed laundry (dermal): Product amount: 6.9 mg Dermal absorption: 4% (unoccluded skin) Hanging machine-washed laundry (inhalation: exposure to vapour-evaporation-increasing release area): Exposure duration: 240 min Amount of solution used: 5000 g Dilution (times) (regular liquid): 1300 Room volume: 20 m^2 Ventilation rate: 0.6 per hour

Exposure Scenario	Assumptions*
	Release area: 10 m^2 Application duration: 17 min Application temperature: 20°C Mass transfer coefficient: 10 m/h Molecular weight matrix: 18 g/mol Combined exposure: (total dermal (mixing and loading + hanging machine washed laundry) + total inhalation (mixing and loading + hanging machine washed laundry)) * 60% (adjusted for the maximum amount of gamma-terpinene in mandarin/tangerine oil)
Non-medicinal ingredient in dietary supplement (adult)	Concentration: 3.53% Amount of mandarin/tangerine oil per capsule: 15 mg (Each package is 12.75 grams and contains 30 capsules. Therefore, each capsule is 425 mg (12.75 grams/30 capsules * 1000 mg/gram). Concentration of mandarin/tangerine oil is 3.53%; 425 mg * 3.53% = 15 mg) Daily dose: 0.254 mg/kg bw/day (based on directions for use which specify 2 capsules per day; 15 mg/capsule * 2 capsules/day * 60% adjustment for gamma-terpinene/70.9 kg (adult body weight)

*Exposure to products was estimated using ConsExpo Web (2016). Exposure estimates were calculated based on default body weights and inhalation rates of 70.9 kg/16.2 m^3/day, 59.4 kg/15.8 m^3/day, 31 kg/14.5 m^3/day, 15.5 kg/9.3 m^3/day, and 7.5 kg/2.1 m^3/day for adults, (20 years and older), adolescents (12 to 19 years old), children (5 to 11 years old), toddlers (6 months to 4 years old), and infants (0 to 6 months old), respectively (HC 1998). Unless specified, the defaults come from the relevant ConsExpo Fact Sheet for the scenario presented.

Appendix F. Exposure parameters used to estimate exposure to alpha-pinene

Table F-1. Exposure parameters for alpha-pinene face mist (10%) scenario

Age Groups*	Product Amount (g/day)[a]	Air Concentraion (24 hrs)[b]	Dermal Exposure (mg/kg bw/day)[c]	Inhalation Exposure (mg/kg bw/day)[d]	Combined Exposure (mg/kg bw/day)[e]
12 to 19 years	0.83	1.4	5.56×10^{-2}	3.72×10^{-1}	4.28×10^{-1}
20+	0.83	1.4	4.66×10^{-2}	3.20×10^{-1}	3.66×10^{-1}

* Only two age groups are applicable for the face mist scenario

[a] Calculated using the upper range of volume per spray of 0.16 mL and the assumption that the maximum number of sprays per day would be 6. Mean product amount (g/day) = 0.16 mL/spray (O.Berg Product Catalog) * 6 sprays/day (upperbound estimate, Harrington – Skincare.com, 2019) * alpha-pinene density (0.86 g/mL) = 0.83 g/day

[b] Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 96% of the applied dose was available for evaporation (amount remaining on the skin surface following dermal absorption of the substance) (96%* product amount/day * 10% concentration), and using the following parameters: exposure duration of 24 hours, emission duration of 1 hour, room volume of 1 m^3 (approximate personal breathing zone), release area equal to surface area of application (assumed equivalent to one-half of head (730 cm^2 for 12-19 yrs, and 637.5 cm^2 for adults as cited in Health Canada 1998), ventilation rate of 2/hr (to approximate

mixing of the personal air space with the room), molelcular weight matrix of 125 g/mol, and application temperature of 37°C.

[c] Dermal exposure calculated using the following formula: [product amount (g/day) *product concentration (10%)*dermal absorption for unoccluded skin (4%)*conversion factor (1000 mg/g)] ÷ body weight (59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998)

[d] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) * Inhalation rate (m^3/day) (15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).

[e] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)

Table F-2. Other exposure scenarios for alpha-pinene (dermal, inhalation, oral)

Exposure Scenario*	Age Group	Concentration or Amount	Dermal Intake (µg/kg bw/day)	Inhalation Exposure (µg/kg bw/day	Oral Intake (µg/kg bw/day)
Mixing, loading, and application of an all-purpose floor cleaner	Adult	1%	2.09	15.45 (68 µg/m^3 – 24 hrs)	N/A
Exposure from contacting cleaned floors	Toddler	1%	0.59	40.58 (68 µg/m^3 – 24 hrs)	1.12
Mixing, loading, and hanging hand-washed laundry	Adult	1%	4.53	12.79 (56 µg/m^3 – 24 hrs)	N/A
Gel air freshener	All sub-populations	5%	N/A	7.99-21 (35 µg/m^3 – 24 hrs)	N/A

* Details on the method and parameters used to estimate inhalation and dermal exposure alpha-pinene from products that are available to consumers are provided in Table F-3.

Table F-3: Exposure parameter assumptions for alpha-pinene

Exposure Scenario	Assumptions*
Mixing, loading and application of an all-purpose floor cleaner (liquid) (adult)	Concentration of alpha-pinene: 1% (assumed maximum concentration when alpha-pinene is used as a fragrance in cleaners). Mixing and loading (dermal): Product amount: 0.01 g Dermal absorption: 4% (unoccluded skin) Mixing and loading (inhalation: exposure to vapour-evaporation-constant release area model) Exposure duration: 0.75 min Product amount: 500 g Room volume: 1 m^3 Ventilation rate: 0.5 per hour Release area: 20 cm^2

Exposure Scenario	Assumptions*
	Emission duration: 0.3 min Application temperature: 20°C Mass transfer coefficient: 10 m/h Molecular weight matrix: 36 g/mol Application (dermal): Product amount: 0.36 g Dermal absorption: 4% (unoccluded skin) Application (inhalation: exposure to vapour-evaporation-increasing release model): Exposure duration: 240 min Amount of solution used: 900 g Dilution (times): 62 Room volume: 58 m^3 Ventilation rate: 0.5 per hour Release area: 22 m^2 Application duration: 20 min Application temperature: 20°C Mass transfer coefficient: 10 m/h Molecular weight matrix: 18 g/mol Combined exposure: total dermal (mixing/loading + application) + total inhalation (mixing/loading + application)
Exposure from contacting cleaned floors (toddler)	Concentration of alpha-pinene: 1% (assumed maximum concentration when alpha-pinene is used as a fragrance in cleaners). Calculations based on the US EPA Residential SOPs (2012), Section 7. Dermal: Calculated using the following algorithm: Exposure (mg/kg bw/day) = [deposited residue (mg/cm^2) * fraction available for transfer (%) * transfer coefficient (cm^2/hr) * exposure time (hrs) * dermal absorption (%)]/body weight Deposited residue (µg/cm^2): Calculated assuming 14.4 g of product per 22 m^2 of floor (ConsExpo Cleaning Fact Sheet, 2018) * 1000 mg/g * 1 m^2/10000 cm^2 Transfer coefficient: 2200 cm^2/hr (adjusted for the surface area of a toddler aged 6 months to 4 years using the following formula; adult transfer coefficient 6800 cm^2/hr * (5780 cm^2 surface area toddler/18200 cm^2 surface area adult)) Fraction available for transfer: 8% Exposure time: 2 hr; exposure time for hard surfaces represents time spent in kitchens and bathrooms Dermal absorption: 4% (unoccluded skin)

Exposure Scenario	Assumptions*
	Incidental Oral (i.e. hand-to-mouth exposure): Calculated using the following algorithm: Exposure (mg/day) = [HR (mg/cm^2) * (F_M * SA_H (cm^2)) * (ET * N_Replen) * (1 – (1 – SE)$^{Freq\_HtM/N\_Replen}$)] HR: hand residue loading (mg/cm^2); calculated using the following algorithm: HR = [Fai_{hands} * Dermal exposure (mg) (calculated above)] / (SA_H * 2) Fai_{hands}: 0.15 (unitless); fraction of active ingredient on hands compared to total surface residue from jazzercise study SA_H: 150 cm^2; typical surface area of one hand F_M: 0.13 (unitless); fraction of hand mouthed per event SA_H: 150 cm^2; typical surface area of one hand ET: 2 hours; exposure time per day N_Replen: 4; number of replenishment intervals per hour SE: 0.48; saliva extraction factor Freq_HtM: 20; number of hand-to-mouth events per hour Inhalation: Air concentration from application of liquid floor cleaner (see above for parameters) Combined exposure: dermal + oral + inhalation
Mixing and loading a liquid for hand washing and hanging hand washed laundry (adult)	Concentration of alpha-pinene: 1% (assumed maximum concentration when alpha-pinene is used as a fragrance in laundry detergent). Mixing and loading (dermal): Product amount: 0.53 g (regular powder) Dermal absorption: 4% (unoccluded skin) Mixing and loading (inhalation-exposure to vapour-evaporation- constant release model): Exposure duration: 0.75 min Amount of solution used: 500 g Room volume: 1 m^3 Ventilation rate: 0.6 per hour Release area: 20 cm^2 Emission duration: 0.3 min Application temperature: 20 °C Mass transfer coefficient: 10 m/h Molecular weight matrix: 90 g/mol Hand-washing (dermal): Product amount: 0.194 g (regular liquid)

Exposure Scenario	Assumptions*
	Dermal absorption: 4% (unoccluded skin) Hand-washing (inhalation – exposure to vapour evaporation – constant release): Exposure duration: 10 minutes Amount of solution used: 15 kg Dilution (times): 110 (regular liquid) Room volume: 20 m^3 Ventilation rate: 0.6 per hour Release area: 1500 cm^2 Emission duration: 10 minutes Application temperature: 40°C Mass transfer coefficient: 10 m/h Molecular weight matrix: 18 g/mol Hanging hand-washed laundry (dermal): Product amount: 79 mg (regular liquid) Dermal absorption: 4% (unoccluded skin) Hanging hand washed laundry (inhalation – exposure to vapour – evaporation – increasing release area): Exposure duration: 240 min Amount of solution : 5 kg Dilution (times): 110 (regular liquid) Room volume: 20 m^3 Ventilation rate: 0.6 per hour Release area: 10 m^2 Application duration: 17 min Application temperature: 20°C Mass transfer coefficient: 10 m/h Molecular weight matrix: 18 g/mol Combined exposure: Dermal (mixing/loading + hand-washing + hanging machine washed laundry) + Inhalation (mixing/loading + hand-washing + hanging machine washed laundry)
Gel air freshener (inhalation)	Concentration of alpha-pinene: 1-5% (SDS, 2016) Scenario: gel air freshener Inhalation: exposure to vapour – instantaneous release scenario Frequency: all day, every day Exposure duration: 24 hour/day Product amount: 1 gel ~ 5.5 mL of product and can last up to 30 days. Assume same amount emitted each day (5.5 mL/30 days = ~ 0.2 mL or 0.2 g/day) Room volume: 20 m^3

Exposure Scenario	Assumptions*
	Ventilation rate: 0.6/hr Exposure (mg/kg bw/day) = (Air concentration (mg/m^3) * daily inhalation rate (m^3/day)) ÷ body weight (kg)

*Exposure to products was estimated using ConsExpo Web (2016). Exposure estimates were calculated based on default body weights and inhalation rates of 70.9 kg/16.2 m^3/day, 59.4 kg/15.8 m^3/day, 31 kg/14.5 m^3/day, 15.5 kg/9.3 m^3/day, and 7.5 kg/2.1 m^3/day for adults, (20 years and older), adolescents (12 to 19 years old), children (5 to 11 years old), toddlers (6 months to 4 years old), and infants (0 to 6 months old), respectively (HC 1998). Unless specified, the defaults come from the relevant ConsExpo Fact Sheet for the scenario presented.

Table F-4. Variable inputs to SCREEN3 for inhalation exposure near an industrial alpha-pinene facility

Variables	Input variables
Source type	Point
Effective emission area [a]	100 × 50 m^2
Emission rate of α-pinene	2.64 (g/s) 83.3×10^6 g/ [(365×24×3600 s)
Receptor height [b]	1.74 m (average adult height)
Stack height [a]	10 m
Stack inside diameter [a]	3 m
Stack gas exit velocity	1 m/s
Stack gas exit temperature	333 K
Ambient air temperature	293 K
Adjustment factor [c]	0.4 (variable wind direction during 24-hour period); 0.2 (average wind direction during 1- year period)
Urban–rural option	Rural
Meteorology [d]	1 (full meteorology)
Minimum and maximum distance	10–3000 m

[a] Professional judgement.
[b] Curry et al. 1993.
[c] US EPA 1992.
[d] Default value in SCREEN3.
[e] The emission of 83.3 tonnes (ECCC 2016b) was converted to (g) then divided by number seconds in a year to estimate and emission rate.

Table F-5. Estimates of alpha-pinene contribution (µg/m^3) to ambient air

Distance (m)	Concentration (µg/m^3) (1 hour)	24 - Hour Concentration (µg/m^3) (multiplied by 0.4)	Annual Concentration (µg/m^3) (multiplied by 0.2)
10	1.32E+04	5.26E+03	2.63E+03
100	713.8	2.86E+02	1.43E+02
200	338.2	1.35E+02	6.76E+01
300	273.2	1.09E+02	5.46E+01

Distance (m)	Concentration (µg/m^3) (1 hour)	24 - Hour Concentration (µg/m^3) (multiplied by 0.4)	Annual Concentration (µg/m^3) (multiplied by 0.2)
400	275	1.10E+02	5.50E+01
500	251.8	1.01E+02	5.04E+01
600	221.9	8.88E+01	4.44E+01
700	193.8	7.75E+01	3.88E+01
800	169.6	6.78E+01	3.39E+01
900	149.4	5.98E+01	2.99E+01
1000	132.6	5.30E+01	2.65E+01
1100	118.6	4.74E+01	2.37E+01
1200	106.9	4.28E+01	2.14E+01
1300	97	3.88E+01	1.94E+01
1400	88.56	3.54E+01	1.77E+01
1500	81.3	3.25E+01	1.63E+01

Appendix F-6. Inhalation Dose Conversions from NTP (2016)

Species	Dose (PPM)	Dose (mg/m^3)[1]	Dose (mg/kg bw/day)[2]	Adjusted Dose (mg/kg bw/day)[3]	Adjusted Dose (mg/m^3)[3]
Mouse[4]	25	139.25	185.67	33.15	24.87
	50	278.50	371.33	66.31	49.73
	100	557	742.67	132.62	99.46
	200	1114	1485.33	265.24	198.93
	400	2228	2970.67	530.48	387.86
Rat[5]	100	557	622.96	111.24	99.46
	200	1114	1245.92	222.49	198.93
	400	2228	2491.84	444.97	397.86
	800	4456	4983.68	889.94	795.74
	1600	8912	9967.37	1779.89	1591.43

[1] At 25°C and 760 mm Hg, 1 g-mole of a perfect gas or vapour occupies 24.45 L. Therefore, under these conditions, the conversion of ppm to mg/m^3 becomes: mg/m^3 = (ppm * molecular weight (g))/24.45. For alpha-pinene, 1 ppm = 5.57 ppm (mg/m^3 = (1 ppm * 136.24)/24.45).

[2] Dose (mg/kg bw/day) was calculated using the following formula: (Concentration (mg/m^3) * Daily Inhalation Rate (m^3/day))/ Body Weight (kg)

[3] Dose was adjusted for exposure conditions in the inhalation study of 6 hours of exposure per day for 5 days per week, and was calculated using the following formula: Adjusted Dose = Dose * (6 hours/24 hours) * (5 days/7 days)

[4] Body weight (0.03 kg) and inhalation rate (0.04 m^3/day) for the mouse is based on HC (1999), Appendix E, and represents an average of both male and female mice.

[5] Body weight (0.152 kg) and inhalation rate (0.17 m^3/day) for the rat is based on US EPA (1988) and represents an average of both male and female Fischer 344 rats.

Appendix G. Exposure parameters used to estimate exposure to turpentine/turpentine oil

Table G-1. Oral exposure parameters for turpentine/turpentine oil from a lip balm

Age Groups	Mean Product Amount (g/app)[a]	Mean Daily Frequency [a]	Product Concentration (%)	Body Weight (kg)[b]	Exposure Dose (mg/kg bw/day)[c]
0-6 months	NA	NA	NA	NA	NA
6 months-4 years	0.01	0.58	0.1	15.5	3.74×10^{-4}
5 to 11 years	0.01	0.89	0.1	31	2.87×10^{-4}
12 to 19 years	0.01	2.35	0.1	59.4	3.96×10^{-4}
20+	0.01	2.35	0.1	70.9	3.31×10^{-4}

[a] As cited in Loretz et al. 2005; Wu et al. 2010
[b] As cited in HC 1998
[d] Assuming oral absorption is equivalent to inhalation

Table G-2. Other exposure scenarios for turpentine oil (dermal, inhalation, oral)

Exposure Scenario*	Age Group	Concentration	Dermal Intake (µg/kg bw/day)	Inhalation Exposure (µg/kg bw/day)	Oral Intake (µg/kg bw/day)
Shoe polish cream	Adult	10%	73.3	25.1 (0.11 mg/m^3 – 24 hrs)	N/A
Paint thinner for oil-based paints	Adult	100%	1168	1.49×10^3 (6.5 mg/m^3 – 24 hrs)	N/A
Paint remover	Adult	100%	282	43 413 (190 mg/m^3 – 24 hrs)	N/A
Furniture Paste Wax	Adult	5%	21.0	45.7 (0.2 mg/m^3 – 24 hrs)	N/A
Car wax	Adult	10%	42.1	251 (1.1 mg/m^3 – 24 hrs)	N/A
Non-medicinal ingredient in topical medicated vapour product	Children (6 mths – 4 yrs)	4.68%	2.04×10^3	4.98×10^3 (8.3 mg/m^3 – 24 hrs)	N/A

Exposure Scenario*	Age Group	Concentration	Dermal Intake (µg/kg bw/day)	Inhalation Exposure (µg/kg bw/day)	Oral Intake (µg/kg bw/day)
Non-medicinal ingredient in topical medicated vapour product	Adult	4.68%	9.94×10^2	4.11×10^3 (18 mg/m^3 – 24 hrs)	N/A
Non-medicinal ingredient in counterirritant product	Children (6 mth – 4 yrs)	25%	4.78×10^3	84.0 (0.14 mg/m^3 – 24 hrs)	N/A
Non-medicinal ingredient in counterirritant product	Adult	25%	2.00×10^3	59.4 (0.26 mg/m^3 – 24 hrs)	N/A

*Details on the method and parameters used to estimate inhalation and dermal exposure to turpentine oil from products that are available to consumers are provided in Table G-3.
N/A Not applicable

Table G-3: Exposure parameter assumptions for turpentine oil

Exposure Scenario	Assumptions*
Shoe polish cream (adult)	Concentration: 10% (Household Products Database, 2018) Dermal: Product amount: 1.3 g Dermal absorption: 4% (unoccluded skin) Inhalation – exposure to vapour - instantaneous release Exposure duration: 240 minutes Product amount: 1.04 g (80% of the dermal product amount) Room volume: 58 m^3 Ventilation rate: 0.6 per hour Application temperature: 20°C Total exposure = dermal + inhalation
Paint thinner for oil-based paints (adult)	Concentration: 100% (MSDS, 2013) Scenario: Paint thinner used to clean paint brushes in a coffee can (1.4 kg). Dermal: Product amount: 2.07 g (Versar 1986) Dermal absorption: 4% (unoccluded skin)

Exposure Scenario	Assumptions*
	Inhalation – exposure to vapour – evaporation model – constant release Exposure duration: 30 minutes (Versar 1986) Product amount: 290 g (US EPA Exposure Factors Handbook 2011) (product amount was estimated from average amounts used per year and the numbers of uses per year; paint thinners are used an average of 6.78 times/year, and an average of 69.45 ounces are used per year, for an estimate of 290 grams/use (69.45 ounces/year ÷ 6.78 uses/year = 10.24 ounces/use or 290 grams)) Room volume: 20 m^3 (RIVM 2014) (unspecified room) Ventilation rate: 0.6 per hour (RIVM 2014) (unspecified room) Mass Transfer coefficient: 10 m/hr Emission duration: 30 minutes Release area: 0.078 m^2 (Versar 1986) (opening of a 1.4 kg coffee can) Molecular weight matrix: 136 g/mol Total exposure = dermal + inhalation
Paint remover (adult)	Concentration: 100% (MSDS, 2013) Scenario: Removal of paint from a door. Remover is applied and left to soak for 15 minutes; afterwards, the resulting putty is removed with a scratching tool. Dermal: Product amount: 0.5 g (RIVM 2007) Dermal absorption: 4% (unoccluded skin) Inhalation – exposure to vapour – evaporation from increasing area (RIVM 2007) Exposure and application duration: 60 minutes Product amount: 1 kg Room volume: 20 m^3 Ventilation rate: 0.6 per hour Release area: 2 m^2 Temperature: 20 °C Molecular weight matrix: 3000 g/mol Total exposure = dermal + inhalation
Furniture Paste Wax (adult)	Concentration: 5% (SDS, 2015a) Scenario: Application of a paste wax to a piece of furniture. Thin-film approach was used as outlined in the EPA-Versar document (Versar 1986, US EPA 2011). Dermal: Film thickness: 1.64 x 10^{-3} cm (mineral oil thickness estimated to remain on skin after wiping) (US EPA 2011)

Exposure Scenario	Assumptions*
	Exposed skin area: 455 cm^2 (half of both hands/palms) Density: 1 g/cm^3 (assumed density of car wax) Dermal absorption: 4% (unoccluded skin) Inhalation – exposure to vapour – evaporation from increasing area Exposure and emission duration: 60 minutes (professional judgement) Product amount: 13.8 g (range of furniture polish was 4.2 – 13.8 g, as a paste wax furniture polish was not included, the maximum product amount was used in the assessment) (Versar 1986) Room volume: 58 m^3 (living room) (RIVM 2014) Ventilation rate: 0.5 per hour (living room) (RIVM 2014) Release area: 1.44 m^2 (surface are of coffee table and end tables) (Versar 1986) Temperature: 20 °C Molecular weight matrix: 216 g/mol (molecular weight of carnauba wax) Total exposure = dermal + inhalation
Car wax (adult)	Concentration: < 10% (SDS, 2013) Scenario: Car wax scenario in a garage. Thin-film approach was used as outlined in the EPA-Versar document (Versar 1986, US EPA 2011). Dermal: Film thickness: 1.64 x 10^{-3} cm (mineral oil thickness estimated to remain on skin after wiping) (Versar 1986) Exposed skin area: 455 cm^2 (half of both hands/palms) Density: 1 g/cm^3 (assumed density of car wax) Dermal absorption: 4% (unoccluded skin) Inhalation – exposure to vapour – evaporation from increasing area Exposure and emission duration: 60 minutes (professional judgement) Product amount: 28 g (approximately 1 ounce of product is used per car wax) (Meguiar's Online Forum, 2010) Room volume: 34 m^3 (garage) (RIVM 2014) Ventilation rate: 1.5 per hour (garage) (RIVM 2014) Release area: 5.57 m^2 (60 ft^2 typical surface area of a car, Jackson - Washington Times, 2008) Temperature: 20 °C Molecular weight matrix: 216 g/mol (molecular weight of carnauba wax) Total exposure = dermal + inhalation

Exposure Scenario	Assumptions*
Non-medicinal ingredient in topical medicated vapour product (toddler, adult)	Concentration: 4.68% Labelling directions: Rub ointment on 3 places: chest, throat, and back. Repeat up to 3-4 times daily, especially at bedtime. Dermal: Product amount (child 6 mths – 4yrs): 0.84 g per application (body lotion value of 4.1 g per use (Ficheux et al. 2015) adjusted by the surface area of the truck divided by 2 to represent the chest, throat, and back). 3.36 g per day (0.84 g/event * 4 events/day) Product amount (adult): 1.88 g per application (body lotion value of 10 g per use (Ficheux et al. 2015) adjusted by the surface area of the truck divided by 2 to represent the chest, throat, and back). 7.52 g per day (1.88 g/event * 4 events/day). Dermal absorption: 20% (occluded skin) Inhalation – exposure to vapour – evaporation model – constant release: Amount available for inhalation: 80% of the above-noted product amount (see dermal absorption summary for more details). Exposure duration: 6 hours (24 hours divided by 4 events per day) Molecular weight matrix: 600 g/mol (petrolatum base) Room volume: 1 m^3 (personal breathing zone) Ventilation rate: 0.6 per hour (unspecified room, RIVM 2014) Mass transfer: 10 m/hr Release area: 3185 cm^2 (adult) (surface area of truck divided by 2 to represent chest, back and throat) 1010 cm^2 (child) (surface area of truck divided by 2 to represent chest, back and throat) Emission duration: 1 hour Inhalation exposure (mg/kg bw/day) = (air concentration (mg/m^3 – 24 hrs) * daily inhalation rate (m^3/day)) ÷ body weight (kg) Total exposure (mg/kg bw/day) = dermal + inhalation
Non-medicinal ingredient in counterirritant product (toddler, adult)	Concentration: 25% Labelling directions: Use up to 4 times daily. Dermal: Product amount (child 6 mths – 4yrs): 0.37 g per application (massage oil value of 1.8 g per use (Ficheux et al. 2016) adjusted by the surface area of the truck divided by 2 to

Exposure Scenario	Assumptions*
	represent the back). 1.48 g per day (0.37 g/event * 4 events/day) Product amount (adult): 0.71 g per application (massage oil value of 3.2 g per use (Ficheux et al. 2016) adjusted by the surface area of the truck divided by 2 to represent the back). 2.84 g per day (0.71 g/event * 4 events/day). Dermal absorption: 20% (occluded skin) Inhalation – exposure to vapour – evaporation model – constant release: Amount available for inhalation: 80% of the above-noted product amount (see dermal absorption summary for more details). Exposure duration: 24 hours Molecular weight matrix: 600 g/mol (petrolatum base) Room volume: 80 m^3 (approximate mixing throughout the day) Ventilation rate: 1 per hour Mass transfer: 10 m/hr Release area: 3185 cm^2 (adult) (surface area of truck divided by 2 to represent chest, back and throat) 1010 cm^2 (child) (surface area of truck divided by 2 to represent chest, back and throat) Emission duration: 1 hour Inhalation exposure (mg/kg bw/day) = (air concentration (mg/m^3 – 24 hrs) * daily inhalation rate (m^3/day)) ÷ body weight (kg) Total exposure (mg/kg bw/day) = dermal + inhalation

*Exposure to products was estimated using ConsExpo Web (2016). Exposure estimates were calculated based on default body weights and inhalation rates of 70.9 kg/16.2 m^3/day, 59.4 kg/15.8 m^3/day, 31 kg/14.5 m^3/day, 15.5 kg/9.3 m^3/day, and 7.5 kg/2.1 m^3/day for adults, (20 years and older), adolescents (12 to 19 years old), children (5 to 11 years old), toddlers (6 months to 4 years old), and infants (0 to 6 months old), respectively (HC 1998). Unless specified, the defaults come from the relevant ConsExpo Fact Sheet for the scenario presented.

Appendix H. Exposure parameters used to estimate exposure to fir oil

Table H-1. Exposure parameters for fir oil body moisturizer (1%) scenario

Age Groups	Mean Product Amount (g/app)[a]	Mean Daily Frequency[b]	Air Conc. (mg/m^3) (24 hrs)[c]	Dermal Exposure (mg/kg bw/day)[d]	Inhalation Exposure (mg/kg bw/day)[e]	Combined Exposure (mg/kg bw/day)[f]
0-6 mths	2.5	0.8	7.6×10^{-3}	5.33×10^{-1}	2.13×10^{-3}	5.35×10^{-1}
6 mths-4 yrs	4.1	0.8	1.2×10^{-2}	4.23×10^{-1}	7.20×10^{-3}	4.30×10^{-1}
5-11 yrs	5	0.8	1.5×10^{-2}	2.58×10^{-1}	7.02×10^{-3}	2.65×10^{-1}

Age Groups	Mean Product Amount (g/app)[a]	Mean Daily Frequency[b]	Air Conc. (mg/m^3) (24 hrs)[c]	Dermal Exposure (mg/kg bw/day)[d]	Inhalation Exposure (mg/kg bw/day)[e]	Combined Exposure (mg/kg bw/day)[f]
12-19 yrs	8.7	0.8	2.6×10^{-2}	2.34×10^{-1}	6.92×10^{-3}	2.41×10^{-1}
20+	10	1	3.8×10^{-2}	2.82×10^{-1}	8.68×10^{-3}	2.91×10^{-1}

[a] As cited in Ficheux et al. 2016

[b] As cited in Ficheux et al. 2015; Wu et al. 2010

[c] Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 80% of the applied dose was available for evaporation (amount remaining on the skin surface following dermal absorption of the substance) (80%* product amount/applications * applications/day * 1% concentration), and using the following parameters: exposure duration of 24 hours, emission duration of 1 hour, room volume of 80 m^3, ventilation rate of 1/hr, surface area equal to exposed skin (assumed equal to head, arms and hands) (1365 cm^2 for 0-6 mths, 1970 cm^2 for 6 mths-4 yrs, 2900 cm^2 for 5-11 yrs, 4540 cm^2 for 12-19 yrs, and 4735 cm^2 for adults as cited in Health Canada 1998), molelcular weight matrix of 125 g/mol, and application temperature of 37°C.

[d] Dermal exposure calculated using the following formula: [mean product (g/application)*mean daily frequency (applications/day)* product concentration (1%) * dermal absorption for occluded skin (20%)*conversion factor (1000 mg/g)] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998)

[e] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) *Inhalation rate (m^3/day) (2.1 m^3/day for 0-6 mths, 9.3 m^3/day for 6 mths-4 yrs, 14.5 m^3/day for 5-11 yrs, 15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).

[f] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)

Table H-2. Dermal exposure parameters for fir oil massage oil (3%) scenario

Age Groups	Mean product amount (g/day)[a]	Air Concentration (24 hrs) (mg/m^3)[b]	Dermal Exposure (mg/kg bw/day)[c]	Inhalation Exposure (mg/kg bw/day)[d]	Combined Exposure (mg/kg bw/day)[e]
0-6 mths	1.8	2.4×10^{-2}	2.88×10^{-1}	6.72×10^{-3}	2.95×10^{-1}
6 mths-4 yrs	1.8	2.4×10^{-2}	1.39×10^{-1}	1.44×10^{-2}	1.54×10^{-1}
5 to 11 yrs	2.5	3.3×10^{-2}	9.68×10^{-2}	1.54×10^{-2}	1.12×10^{-1}
12 to 19 yrs	2.9	3.8×10^{-2}	5.86×10^{-2}	1.01×10^{-2}	6.87×10^{-2}
20+	3.2	4.2×10^{-2}	5.42×10^{-2}	9.60×10^{-3}	6.38×10^{-2}

[a] As cited in Ficheux et al. 2016. Assumed frequency of 1 massage per day. Concentration of fir oil is based on the upper concentration of essential oils in massage oil (RIVM, 2006).

[b] Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 96% of the applied dose was available for evaporation (amount remaining on the skin surface following dermal absorption of the substance) (96%* product amount/day * concentration of massage oil (3%)), and using the following parameters: exposure duration of 24 hours, emission duration of 1 hour, room volume of 80 m^3, ventilation rate of 1/hr, release area equal to exposed surface area (total surface area minus head for 0-11 years and total surface area minus one-half head and trunk for adults and adolescents) (3020 cm^2 for 0-6 mths, 4910 cm^2 for 6 mths-4 yrs, 8450 cm^2 for 5-11 yrs, 12795 cm^2 for 12-19 yrs, and 14380 cm^2 for 20+ yrs as cited in Health Canada 1998), molelcular weight matrix of 125 g/mol, and application temperature of 37°C.

[c] Dermal exposure calculated using the following formula: [mean product (g/day) * concentration of massage oil (3%) * dermal absorption for unoccluded skin (4%)*conversion factor (1000 mg/g)] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998)

[d] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) * Inhalation rate (m^3/day) (2.1 m^3/day for 0-6 mths, 9.3 m^3/day for 6 mths-4 yrs, 14.5 m^3/day for 5-11 yrs, 15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).
[e] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)

Table H-3. Exposure parameters for fir oil face moisturizer (3%) scenario

Age Groups*	Product Amount (g/use)[a]	Uses per Day[a]	Air Concentraion (24 hrs)[b]	Dermal Exposure (mg/kg bw/day)[c]	Inhalation Exposure (mg/kg bw/day)[d]	Combined Exposure (mg/kg bw/day)[e]
12 to 19 years	1.5	1	7.8×10^{-1}	3.03×10^{-2}	2.07×10^{-1}	2.38×10^{-1}
20+	1.5	2	1.6	5.08×10^{-2}	3.66×10^{-1}	4.16×10^{-1}

* Only two age groups are applicable for the face moisturizer scenario
[a] As cited in Ficheux et al. 2016; Ficheux et al. 2015; and Loretz et al. 2005
[b] Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 96% of the applied dose was available for evaporation (amount remaining on the skin surface following dermal absorption of the substance) (96%* product amount/day * 3% concentration), and using the following parameters: exposure duration of 24 hours, emission duration of 1 hour, room volume of 1 m^3 (approximate personal breathing zone), release area equal to surface area of application (assumed equivalent to one-half of head (730 cm^2 for 12-19 yrs, and 637.5 cm^2 for adults as cited in Health Canada 1998), ventilation rate of 2/hr (to approximate mixing of the personal air space with the room), molelcular weight matrix of 125 g/mol, and application temperature of 37°C.
[c] Dermal exposure calculated using the following formula: [product amount (g/day) *product concentration (3%)*dermal absorption for unoccluded skin (4%)*conversion factor (1000 mg/g)] ÷ body weight (59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998)
[d] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) * Inhalation rate (m^3/day) (15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).
[e] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)

Table H-4. Inhalation exposure parameters for fir oil perfume (100%) scenario (instantaneous release)

Age Groups	Mean Product Amount (g/app)[a]	Mean Daily Frequency[a]	Air Concentration (mg/m^3) (24hr)[b]	Exposure (mg/kg bw/day)[c]
5 to 11 years	0.33	1.7	0.19	8.89×10^{-2}
12 to 19 years	0.33	1.7	0.19	5.05×10^{-2}
20+	0.33	1.7	0.19	4.34×10^{-2}

[a] As cited in Loretz et al. 2005
[b] ConsExpo parameters used= exposure duration of 5 min, room volume of 10m^3 (bathroom), 0 per hour ventilation rate
[c] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) *Inhalation rate (m^3/day) (14.5 m^3/day for 5-11 yrs, 15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).

Table H-5. Other exposure scenarios for fir oil (dermal, inhalation, oral)

Exposure Scenario*	Age Group	Concentration	Dermal Intake (mg/kg bw/day)	Inhalation Exposure (mg/kg bw/day)	Oral Intake (mg/kg bw/day)
Air freshener (wax melt)	All sub-populations	5%	N/A	1.65×10^{-1} – 4.32×10^{-1} (0.72 mg/m^3 – 24 hrs)	N/A
Non-medicinal ingredient in liquid cold medication	Adult – Children 3+	0.27%	N/A	N/A	1.14 - 2.61
Chest balm product	Adult - Infant	3%	1.59×10^{-1} – 3.27×10^{-1}	6.63×10^{-1} – 7.80×10^{-1} (1.30 – 2.90 mg/m^3 – 24 hrs)	N/A

*****Details on the method and parameters used to estimate inhalation and dermal exposure to fir oil from products that are available to consumers are provided in Table H-5.

Table H-6. Exposure parameter assumptions for fir oil

Exposure Scenario	Assumptions*
Air freshener (wax melt) (inhalation) (all sub-populations)	Concentration of fir oil: 1-5% (SDS, 2015b) Inhalation – exposure to vapour, constant rate scenario Exposure duration: 4 hours (air freshener scenario in ConsExpo Cosmetics Fact Sheet (RIVM 2006)) Product amount: each wax melt contains 78 grams of product and lasts for approximately 16 hours; one event equals 3 hours or 14.63 g of product (78 grams/16 hours * 3 hours/day) Room volume: 58 m^3 (living room) (air freshener scenario in ConsExpo Cosmetics Fact Sheet (RIVM 2006)) Ventilation rate: 0.5/hr (living room) (air freshener scenario in ConsExpo Cosmetics Fact Sheet (RIVM 2006)) Emission duration: 3 hours (air freshener scenario in ConsExpo Cosmetics Fact Sheet (RIVM 2006)) Inhalation exposure (mg/kg bw/day) = (air concentration (mg/m^3 – 24 hrs) * daily inhalation rate (m^3/day)) ÷ body weight (kg)
Non-medicinal ingredient in liquid cold medication (children 3+ and adults)	Concentration of fir oil: 0.27% (personal communication with NNHPD) Label Directions:

Exposure Scenario	Assumptions*
	Children 3-9 yrs: 5 mL up to 3 times daily for 4 to 5 days (0.27% * 5 mL * 3 times/day * 1 g/mL (assumed density of syrup)/ 15.5 kg (body weight 6 mths – 4 yrs) = 2.61 mg/kg bw/day) Adults: 10 mL up to 3 times daily for 4 to 5 days (0.27% * 10 mL * 3 times/day * 1 g/mL (assumed density of syrup)/ 70.9 kg (body weight adult) = 1.14 mg/kg bw/day)
Chest balm product (all age groups)	Concentration: 1-3% (personal communication with Consumer Products Safety Directorate, 2019) Labelling directions: One application per day. Apply a small quantity of gel and rub on back and chest before going to bed (personal communication with Consumer Products Safety Directorate, 2019). Dermal: Product amount (child 6 mths – 4yrs): 0.84 g per application (body lotion value of 4.1 g per use (Ficheux et al. 2015) adjusted by the surface area of the truck divided by 2 to represent the chest, throat, and back). 3.36 g per day (0.84 g/event * 1 event/day) Product amount (adult): 1.88 g per application (body lotion value of 10 g per use (Ficheux et al. 2015) adjusted by the surface area of the truck divided by 2 to represent the chest, throat, and back). 7.52 g per day (1.88 g/event * 1 event/day). Dermal absorption: 20% (occluded skin) Inhalation – exposure to vapour – evaporation model – constant release: Amount available for inhalation: 80% of the above-noted product amount (see dermal absorption summary for more details). Exposure duration: 24 hours Molecular weight matrix: 600 g/mol (petrolatum base) Room volume: 1 m^3 (personal breathing zone) Ventilation rate: 0.6 per hour (unspecified room, RIVM 2014) Mass transfer: 10 m/hr Release area: 3185 cm^2 (adult) (surface area of truck divided by 2 to represent chest, back and throat) 1010 cm^2 (child) (surface area of truck divided by 2 to represent chest, back and throat) Emission duration: 1 hour Inhalation exposure (mg/kg bw/day) = (air concentration (mg/m^3 – 24 hrs) * daily inhalation rate (m^3/day)) ÷ body weight (kg) Total exposure (mg/kg bw/day) = dermal + inhalation

*Exposure to products was estimated using ConsExpo Web (2016). Exposure estimates were calculated based on default body weights and inhalation rates of 70.9 kg/16.2 m^3/day, 59.4 kg/15.8 m^3/day, 31 kg/14.5 m^3/day, 15.5 kg/9.3

m^3/day, and 7.5 kg/2.1 m^3/day for adults, (20 years and older), adolescents (12 to 19 years old), children (5 to 11 years old), toddlers (6 months to 4 years old), and infants (0 to 6 months old), respectively (HC 1998). Unless specified, the defaults come from the relevant ConsExpo Fact Sheet for the scenario presented.

Appendix I. Exposure parameters used to estimate exposure to pine oil

Table I-1. Exposure parameters for pine oil body moisturizer (0.3%) scenario

Age Groups	Mean Product Amount (g/app)[a]	Mean Daily Frequency[b]	Air Conc. (mg/m^3) (24 hrs)[c]	Dermal Exposure (mg/kg bw/day)[d]	Inhalation Exposure (mg/kg bw/day)[e]	Combined Exposure (mg/kg bw/day)[f]
0-6 mths	2.5	0.8	2.3×10^{-3}	1.60×10^{-1}	6.44×10^{-4}	1.61×10^{-1}
6 mths-4 yrs	4.1	0.8	3.7×10^{-3}	1.27×10^{-1}	2.22×10^{-3}	1.29×10^{-1}
5-11 yrs	5	0.8	4.5×10^{-3}	7.74×10^{-2}	2.10×10^{-3}	7.95×10^{-2}
12-19 yrs	8.7	0.8	7.9×10^{-3}	7.03×10^{-2}	2.10×10^{-3}	7.24×10^{-2}
20+	10	1	1.2×10^{-2}	8.46×10^{-2}	2.74×10^{-3}	8.74×10^{-2}

[a] As cited in Ficheux et al. 2016

[b] As cited in Ficheux et al. 2015; Wu et al. 2010

[c] Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 80% of the applied dose was available for evaporation (amount remaining on the skin surface following dermal absorption of the substance) (80%* product amount/applications * applications/day * 0.3% concentration), and using the following parameters: exposure duration of 24 hours, emission duration of 1 hour, room volume of 80 m^3, ventilation rate of 1/hr, surface area equal to exposed skin (assumed equal to head, arms and hands) (1365 cm^2 for 0-6 mths, 1970 cm^2 for 6 mths-4 yrs, 2900 cm^2 for 5-11 yrs, 4540 cm^2 for 12-19 yrs, and 4735 cm^2 for adults as cited in Health Canada 1998), molelcular weight matrix of 125 g/mol, and application temperature of 37°C.

[d] Dermal exposure calculated using the following formula: [mean product (g/application)*mean daily frequency (applications/day)* product concentration (0.3%) * dermal absorption for occluded skin (20%)*conversion factor (1000 mg/g)] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998)

[e] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) *Inhalation rate (m^3/day) (2.1 m^3/day for 0-6 mths, 9.3 m^3/day for 6 mths-4 yrs, 14.5 m^3/day for 5-11 yrs, 15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).

[f] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)

Table I-2. Dermal exposure parameters for pine oil massage oil (1%) scenario

Age Groups	Mean product amount (g/day)[a]	Air Concentration (24 hrs) (mg/m^3)[b]	Dermal Exposure (mg/kg bw/day)[c]	Inhalation Exposure (mg/kg bw/day)[d]	Combined Exposure (mg/kg bw/day)[e]
0-6 mths	1.8	8.0×10^{-3}	9.60×10^{-2}	2.24×10^{-3}	9.82×10^{-2}
6 mths-4 yrs	1.8	8.0×10^{-3}	4.65×10^{-2}	4.80×10^{-3}	5.13×10^{-2}
5 to 11 yrs	2.5	1.1×10^{-2}	3.23×10^{-2}	5.15×10^{-3}	3.74×10^{-2}

Age Groups	Mean product amount (g/day)[a]	Air Concentration (24 hrs) (mg/m^3)[b]	Dermal Exposure (mg/kg bw/day)[c]	Inhalation Exposure (mg/kg bw/day)[d]	Combined Exposure (mg/kg bw/day)[e]
12 to 19 yrs	2.9	1.3×10^{-2}	1.95×10^{-2}	3.46×10^{-3}	2.30×10^{-2}
20+	3.2	1.4×10^{-2}	1.81×10^{-2}	3.20×10^{-3}	2.13×10^{-2}

[a] As cited in Ficheux et al. 2016. Assumed frequency of 1 massage per day.

[b] Air concentrations were modelled using ConsExpo exposure to vapour-evaporation-constant release model, assuming 96% of the applied dose was available for evaporation (amount remaining on the skin surface following dermal absorption of the substance) (96%* product amount/day * concentration of massage oil (1%)), and using the following parameters: exposure duration of 24 hours, emission duration of 1 hour, room volume of 80 m^3, ventilation rate of 1/hr, release area equal to exposed surface area (total surface area minus head for 0-11 years and total surface area minus one-half head and trunk for adults and adolescents) (3020 cm^2 for 0-6 mths, 4910 cm^2 for 6 mths-4 yrs, 8450 cm^2 for 5-11 yrs, 12795 cm^2 for 12-19 yrs, and 14380 cm^2 for 20+ yrs as cited in Health Canada 1998), molelcular weight matrix of 125 g/mol, and application temperature of 37°C.

[c] Dermal exposure calculated using the following formula: [mean product (g/day) * concentration of massage oil (1%) * dermal absorption for unoccluded skin (4%)*conversion factor (1000 mg/g)] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998)

[d] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) * Inhalation rate (m^3/day) (2.1 m^3/day for 0-6 mths, 9.3 m^3/day for 6 mths-4 yrs, 14.5 m^3/day for 5-11 yrs, 15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (7.5 kg for 0-6 mths, 15.5 kg for 6 mths-4 yrs, 31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).

[e] Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)

Table I-3. Inhalation exposure parameters for pine oil perfume (100%) scenario (instantaneous release)

Age Groups	Mean Product Amount (g/app)[a]	Mean Daily Frequency[a]	Air Concentration (mg/m^3) (24hr)[b]	Exposure (mg/kg bw/day)[c]
5 to 11 years	0.33	1.7	0.19	8.89×10^{-2}
12 to 19 years	0.33	1.7	0.19	5.05×10^{-2}
20+	0.33	1.7	0.19	4.34×10^{-2}

[a] As cited in Loretz et al. 2005

[b] ConsExpo parameters used= exposure duration of 5 min, room volume of 10m^3 (bathroom), 0 per hour ventilation rate

[c] Inhalation exposure calculated using the following formula: [Air concentration (mg/m^3) (24 hrs time-weighted average) *Inhalation rate (m^3/day) (14.5 m^3/day for 5-11 yrs, 15.8 m^3/day for 12-19 yrs, and 16.2 m^3/day for 20+ yrs as cited in Health Canada 1998] ÷ body weight (31.0 kg for 5–11 yrs, 59.4 kg for 12-19 yrs, and 70.9 kg for 20+ yrs as cited in Heath Canada 1998).

Table I-4. Other exposure scenarios for pine oil (dermal, inhalation, oral)

Exposure Scenario*	Age Group	Concentration	Dermal Intake (µg/kg bw/day)	Inhalation Exposure (µg/kg bw/day)	Oral Intake (µg/kg bw/day)
Mixing, loading, and application of an all-purpose floor cleaner	Adult	5%	10.4	77.7 (340 µg/m^3 – 24 hrs)	N/A
Exposure from contacting cleaned floors	Toddler	5%	2.97	204 (340 µg/m^3 – 24 hrs)	5.58
Automatic Toilet Bowl Cleaner	Toddler-Adult	10%	N/A	66.3 – 174 (290 µg/m^3 – 24 hrs)	N/A
NMI in Natural Health Products	Adult - Adolescent	4 mg/mL	N/A	N/A	2 820 – 3 370

*Details on the method and parameters used to estimate inhalation and dermal exposure to pine oil from products that are available to consumers are provided in Table I-5.

Table I-5. Exposure parameter assumptions for pine oil

Exposure Scenario	Assumptions*
Mixing, loading and application of an all-purpose floor cleaner (liquid) (adult)	Concentration of pine oil: 5% (MSDS, 2015) Mixing and loading (dermal): Produce amount: 0.01 g Dermal absorption: 4% (unoccluded skin) Mixing and loading (inhalation: exposure to vapour-evaporation-constant release area model) Exposure duration: 0.75 min Product amount: 500 g Room volume: 1 m^3 Ventilation rate: 0.5 per hour Release area: 20 cm^2 Emission duration: 0.3 min Application temperature: 20°C Mass transfer coefficient: 10 m/h Molecular weight matrix: 36 g/mol Application (dermal): Product amount: 0.36 g Dermal absorption: 4% (unoccluded skin)

Exposure Scenario	Assumptions*
	Application (inhalation: exposure to vapour-evaporation-increasing release model) Exposure duration: 240 min Amount of solution used: 900 g Dilution (times): 62 Room volume: 58 m^3 Ventilation rate: 0.5 per hour Release area: 22 m^2 Application duration: 20 min Application temperature: 20°C Mass transfer coefficient: 10 m/h Molecular weight matrix: 18 g/mol Combined exposure: total dermal (mixing/loading + application) + total inhalation (mixing/loading + application)
Exposure from contacting cleaned floors (toddler)	Concentration of pine oil: 5% (MSDS, 2015) Calculations based on the US EPA Residential SOPs (2012a), Section 7. Dermal: Calculated using the following algorithm: Exposure (mg/kg bw/day) = [deposited residue (mg/cm^2) * fraction available for transfer (%) * transfer coefficient (cm^2/hr) * exposure time (hrs) * dermal absorption (%)]/body weight Deposited residue (µg/cm^2): Calculated assuming 14.4 g of product per 22 m^2 of floor (ConsExpo Cleaning Fact Sheet, 2018) * 1000 mg/g * 1 m^2/10000 cm^2 Transfer coefficient: 2200 cm^2/hr (adjusted for the surface area of a toddler aged 6 months to 4 years using the following formula; adult transfer coefficient 6800 cm^2/hr * (5780 cm^2 surface area toddler/18200 cm^2 surface area adult)) Fraction available for transfer: 8% Exposure time: 2 hr; exposure time for hard surfaces represents time spent in kitchens and bathrooms Dermal absorption: 4% (unoccluded skin) Incidental Oral (i.e. hand-to-mouth exposure): Calculated using the following algorithm: Exposure (mg/day) = [HR (mg/cm^2) * (F_M * SA_H (cm^2)) * (ET * N_Replen) * (1 – (1 – SE)$^{Freq\_HtM/N\_Replen}$)] HR: hand residue loading (mg/cm^2); calculated using the following algorithm: HR = [Fai_{hands} * Dermal exposure (mg) (calculated above)] / (SA_H * 2)

Exposure Scenario	Assumptions*
	Fai_{hands}: 0.15 (unitless); fraction of active ingredient on hands compared to total surface residue from jazzercise study SA_H: 150 cm^2; typical surface area of one hand F_M: 0.13 (unitless); fraction of hand mouthed per event SA_H: 150 cm^2; typical surface area of one hand ET: 2 hours; exposure time per day N_Replen: 4; number of replenishment intervals per hour SE: 0.48; saliva extraction factor Freq_HtM: 20; number of hand-to-mouth events per hour Inhalation: Air concentration from application of liquid floor cleaner (see above for parameters) Combined exposure: dermal + oral + inhalation
Automatic toilet bowl cleaner (toilet rim block scenario in ConsExpo) (adult)	Concentration of pine oil: 10% (MSDS, 2008) Dermal – exposure expected to be minimal Inhalation – exposure to vapour-instant release model Exposure duration: 50 minutes Solid rim block: 0.21 g Room volume: 2.5 m^3 Ventilation: 0 per hour
Non-medicinal ingredient in natural health product (adult, adolescent)	Amount of pine oil: 20 mg per 5 mL (teaspoon) Daily exposure (adult): (20 mg/teaspoon* 2 teaspoons/dose * 5 doses/day)/ Body weight (70.9 kg-adult or 59.4 kg-adolescent) = 2.82 mg/kg bw/day (adult), 3.37 mg/kg bw/day (adolescent)

*Exposure to products was estimated using ConsExpo Web (2016). Exposure estimates were calculated based on default body weights and inhalation rates of 70.9 kg/16.2 m^3/day, 59.4 kg/15.8 m^3/day, 31 kg/14.5 m^3/day, 15.5 kg/9.3 m^3/day, and 7.5 kg/2.1 m^3/day for adults, (20 years and older), adolescents (12 to 19 years old), children (5 to 11 years old), toddlers (6 months to 4 years old), and infants (0 to 6 months old), respectively (HC 1998). Unless specified, the defaults come from the relevant ConsExpo Fact Sheet for the scenario presented.