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Draft Assessment

Terpenes and Terpenoids

Phenylpropanoids and Aldehydes Group

**Environment and Climate Change Canada
Health Canada**

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Synopsis

Pursuant to section 68 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted an assessment on 12 substances referred to under the Chemicals Management Plan as the Phenylpropanoids and Aldehydes Group. The Chemical Abstracts Service Registry Numbers (CAS RNs¹), their *Domestic Substances List* (DSL) names, their common names, and their subgroupings used in this assessment are listed in the table below.

Substances in the Phenylpropanoids and Aldehydes Group

CAS RN	Subgroup	DSL name	Common name
8006-78-8 ^a	Individual (Phenylpropanoids)	Oils, bay	Bay oil
8016-88-4 ^a	Individual (Phenylpropanoids)	Oils, tarragon	Tarragon oil
8022-96-6 ^a	Phenylpropanoids subgroup 1 (Phenylpropanoids)	Oils, jasmine	Jasmine oil
8024-43-9 ^a	Phenylpropanoids subgroup 1 (Phenylpropanoids)	Perfumes and essences, jasmin	Perfumes and essences of jasmin
8024-08-6 ^a	Individual (Aldehydes)	Oils, violet	Violet oil
80-54-6	Aldehydes subgroup 2 (Aldehydes)	Benzenepropanol, 4-(1,1- dimethylethyl)- α -methyl-	Lilial
91-51-0	Aldehydes subgroup 2 (Aldehydes)	Benzoic acid, 2-[[3-[4-(1,1- dimethylethyl)phenyl]-2- methylpropylidene]amino]-, methyl ester	Verdantiol
37677-14-8	Aldehydes subgroup 2 (Aldehydes)	3-Cyclohexene-1- carboxaldehyde, 4-(4-methyl- 3-pentenyl)-	Myrac-aldehyde
52474-60-9	Aldehydes subgroup 2 (Aldehydes)	3-Cyclohexene-1- carboxaldehyde, 1-methyl-3- (4-methyl-3-pentenyl)-	Myrmac-aldehyde

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CAS RN	Subgroup	DSL name	Common name
52475-86-2	Aldehydes subgroup 2 (Aldehydes)	3-Cyclohexene-1-carboxaldehyde, 1-methyl-4-(4-methyl-3-pentenyl)-	Myrmac-carboxaldehyde
65405-84-7	Aldehydes subgroup 2 (Aldehydes)	Cyclohexenebutanal, α ,2,2,6-tetramethyl-	Cetonal
66327-54-6	Aldehydes subgroup 2 (Aldehydes)	3-Cyclohexene-1-carboxaldehyde, 1-methyl-4-(4-methylpentyl)-	Vernaldehyde

^a This substance is a UVCB (substance of unknown or variable composition, complex reaction products, or biological materials).

All of the substances in the Phenylpropanoids and Aldehydes Group were included in a survey issued pursuant to a CEPA section 71 survey (Canada 2012). With the exception of lilial, none of the substances in this group were reported to be manufactured or imported into Canada in quantities greater than the reported threshold of 100 kg during the 2011 reporting year (Environment Canada 2013). For lilial, 910 kg was reported to be manufactured in Canada in 2008, and 24 460 kg was reported to be imported into Canada during the same calendar year (Environment Canada 2013).

The substances in the Phenylpropanoids and Aldehydes Group are generally used as fragrance ingredients in cosmetics, drugs including natural health products (NHPs), cleaning products, and air fresheners, including do-it-yourself (DIY) use of these substances to create some of these products. Some of them are also present in pest control products as formulants. In addition, some of them occur naturally in food and may be used as food flavouring agents.

The ecological risks of substances in the Phenylpropanoids and Aldehydes 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, the substances in the Phenylpropanoids and Aldehydes Group are considered unlikely to be causing ecological harm.

Considering all available lines of evidence presented in this draft assessment, there is low risk of harm to the environment from substances in the Phenylpropanoids and

Aldehydes Group. It is proposed to conclude that the 12 substances in the Phenylpropanoids and Aldehydes Group do not meet the criteria under paragraphs 64(a) or (b) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

For the human health risk assessment, 9 of the 12 substances in this group have been addressed under two subgroups, due to similarities in chemical structure, properties, and/or toxicity, while the remaining 3 substances were addressed individually. An impact on human health resulting from exposure to these substances from environmental media is not expected due to the low quantities submitted in response to a CEPA section 71 survey or estimated exposures from environmental monitoring and modelling. Where applicable, exposures were characterized for the use of cosmetics, drugs including NHPs, possible use as food flavouring agents, cleaning products, air fresheners, and DIY products containing the phenylpropanoids and aldehydes, and were expected to be predominately by the dermal and inhalation routes.

For bay oil, the risk characterization was based on methyl eugenol, a component of bay oil. The critical health effect was genotoxic carcinogenicity in laboratory animals. Methyl eugenol is described as a restricted ingredient on the Cosmetic Ingredient Hotlist. The Cosmetic Ingredient Hotlist describes it as being permitted only as a naturally occurring component in botanical extracts, with maximum permitted concentrations in the final product listed for different product types. In this assessment, it has been assumed that these restrictions are met and that bay oil is the only contributor of methyl eugenol. Margins of exposure (MOEs) to bay oil from food, cosmetics, and a respiratory air spray or inhaler stick (NHP) are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk. A comparison of the critical health effect to the estimated level of exposure to bay oil from its use in making a DIY bath oil product is considered adequate to address uncertainties in the health effects and exposure data used to characterize risk. The MOEs to bay oil from its use in DIY products such as in aromatic diffusers or body moisturizer, with the critical health effect, are considered potentially inadequate to account for uncertainties in the health effects and exposure data used to characterize risk.

For tarragon oil, the risk characterization was based on one of its main components, methyl eugenol, and two structurally similar compounds, estragole and elemicin, which were assumed in this assessment to have the same cancer potency as methyl eugenol. The critical health effect was genotoxic carcinogenicity in laboratory animals. The MOEs to tarragon oil from food (based on its potential use as a flavouring agent), digestive aid capsules (NHP), facial cleanser, and soap are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk. However, the MOEs between the critical effect level and the estimates of daily exposure from body moisturizer, body fragrance, and facial moisturizer are considered potentially inadequate to account for uncertainties in the health effects and exposure data used to characterize risk. In addition, for exposures to tarragon oil from its use in DIY products

such as in aromatic diffusers, massage oil, bath oil product, or body moisturizer, the MOEs are considered potentially inadequate to account for uncertainties in the health effects and exposure data used to characterize risk.

For phenylpropanoids subgroup 1 (jasmine oil, perfumes and essences of jasmin), hazard information was based on jasmine extract. The critical health effect was female reproductive toxicity in laboratory animals. A comparison of the critical health effect to estimated levels of exposure to phenylpropanoids subgroup 1 from food (based on its potential use as a flavouring agent), hair conditioner, body cleanser, topical treatment cream (NHP), facial sun protection powder (NHP), de-stress roll-on (NHP), lipstick, hair styling product, antiperspirant/deodorant, temporary hair colour, and sunscreen (children of 2 years and older) (NHP) resulted in MOEs that are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk. In addition, MOEs for jasmine oil from its use in a DIY bath oil product are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk. The MOEs derived from the use of jasmine oil in an aerosol all-purpose cleaner, all-purpose floor cleaner, aerosol laundry conditioner, or a liquid laundry detergent are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk. However, the MOEs between the critical effect levels and the estimates of daily exposure from body moisturizer, body fragrance, facial moisturizer/acne treatment (NHP), sunscreen (children who are 6 to 12 months old) (NHP), or antiseptic skin cleanser (NHP) are considered potentially inadequate to account for uncertainties in the health effects and exposure data used to characterize risk. In addition, the MOEs derived from the use of jasmine oil in DIY products such as in aromatic diffusers, massage oil, body moisturizer, or facial steamer are considered potentially inadequate to account for uncertainties in the health effects and exposure data used to characterize risk.

Hazard information for 2,4-hexadienal, the read-across analogue of 2,6-nonadienal, one of the main components of violet oil, was used to inform the hazard assessment of violet oil. Critical health effects in laboratory animals of mild to moderate forestomach epithelial hyperplasia were used to characterize risk. The MOEs to violet oil from food (based on its potential use as a flavouring agent), eye moisturizer, hair conditioner, facial cleanser, body moisturizer, massage oil (people who are 9 years and above), lipstick, body fragrance, or its use in DIY products such as a bath oil product or body moisturizer are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk. However, the MOEs derived from the use of violet oil in a massage oil (children who are 8 years and below) and the use of violet oil in DIY products, such as those used in aromatic diffusers or facial steamers, are considered potentially inadequate to account for uncertainties in the health effects and exposure data used to characterize risk.

For aldehydes subgroup 2 (lilial, verdantiol, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, vernaldehyde), hazard information for lilial was used as a read-across analogue to inform the hazard assessment for all the other substances in the aldehydes subgroup. Critical health effects of developmental toxicity in laboratory

animals were used to characterize risk. The MOEs between the critical effect levels and the estimates of exposure to lilial from environmental media, body cleanser, hair conditioner (wash-off), face makeup, nail polish, nail polish remover, depilator product, spray antiperspirant/deodorant, bath product, acne treatment (NHP), antiseptic skin cleanser (NHP), temporary hair colour, or facial sunless tanning product are considered to be adequate to account for uncertainties in the health effects and exposure data used to characterize risk. In addition, the MOEs between the critical effect levels and the estimates of exposure to lilial from a carpet deodorizer are considered to be adequate to account for uncertainties in the health effects and exposure data used to characterize risk. However, the MOEs between the critical effect levels and the estimates of daily exposure to lilial from cosmetics, solid gel air freshener, or a liquid plug-in air freshener (1 year old children) are considered potentially inadequate to account for uncertainties in the health effects and exposure data used to characterize risk.

For myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde, the MOEs between the critical effect level and the estimates of daily exposure from cosmetics, as well as air fresheners and cleaning products, are considered adequate to account for uncertainties.

Since there were no identified sources of exposure to the general population for verdantol, a qualitative approach to risk characterization was taken, and the risk to human health from verdantol was considered to be low.

The human health assessment for each substance took into consideration those groups of individuals within the Canadian population who, due to greater susceptibility or greater exposure, may be more vulnerable to experiencing adverse health effects. Certain subpopulations are routinely considered throughout the assessment process, such as infants, children, and people of reproductive age. For instance, age-specific exposures are routinely estimated, and developmental and reproductive studies are evaluated for potential adverse health effects. These subpopulations that have potential for higher exposure and those who may be more susceptible were taken into account in the risk assessment outcomes.

On the basis of the information presented in this draft assessment, it is proposed to conclude that bay oil, tarragon oil, jasmine oil, perfumes and essences of jasmine, violet oil, and lilial 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 and that verdantol, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde do not meet the criteria under paragraph 64(c) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is proposed to conclude that bay oil, tarragon oil, jasmine oil, perfumes and essences of jasmine, violet oil, and lilial meet one or more of the criteria set out in section 64 of CEPA and that verdantol, myrac-aldehyde, myrmac-aldehyde, myrmac-

carboxaldehyde, cetonal, and vernaldehyde do not meet any of the criteria set out in section 64 of CEPA.

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

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1. Introduction

Pursuant to section 68 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have conducted an assessment on 12 of 76 substances, referred to collectively under the Chemicals Management Plan (CMP) as the Terpenes and Terpenoids Group, to determine whether these 12 substances present or may present a risk to the environment or to human health. These 12 substances were identified as priorities for assessment as they met categorization criteria or were considered a priority through other mechanisms (ECCC, HC [modified 2017]).

Of the other substances in the Terpenes and Terpenoids Group, 33 have been assessed in terms of risk to ecological and human health, and the decisions for these substances are provided in separate reports.² Chemical Abstracts Service Registry Number (CAS RN)³ 91-51-0 was identified as a priority for assessment as it met categorization criteria and is being included in this assessment because its chemical properties are similar to those of other priority substances included herein. Decisions on the remaining substances will be communicated in separate assessments.

The 12 substances addressed in this assessment will hereinafter be referred to as the Phenylpropanoids and Aldehydes Group. Some substances are assessed in subgroups due to their similarities in chemical structure, properties, and/or toxicity. Given the potential for these substances to be used in similar ways and applications, the potential for risk to human health is assessed using similar exposure assumptions across the subgroups.

The ecological risks posed by the substances in the Phenylpropanoids and Aldehydes Group were characterized using the ecological risk classification of organic substances (ERC) approach (ECCC 2016a). The ERC describes the hazard of a substance using key metrics, including mode of toxic action, chemical reactivity, food web-derived

² The conclusion for CAS RN 25428-43-7 is provided in the Rapid Screening of Substances with Limited General Population Exposure Screening Assessment (ECCC, HC 2018a). The conclusions for CAS RNs 29350-73-0 and 68916-97-2 are provided in the Substances Identified as Being of Low Concern using the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Screening Assessment (ECCC, HC 2018b). The proposed conclusions for the following 15 substances are provided in the Acyclic, Monocyclic, and Bicyclic Monoterpenes Group Screening Assessment: CAS RNs 80-56-8, 1113-21-9, 8000-46-2, 8002-09-3, 8006-64-2, 8007-01-0, 8007-02-1, 8008-31-9, 8008-52-4, 8008-57-9, 8014-19-5, 8015-77-8, 8016-85-1, 8021-28-1, and 9005-90-7. The proposed conclusions for the following 16 substances are provided in the Monocyclic and Bicyclic Sesquiterpenes Group Screening Assessment: CAS RNs 8007-08-7, 495-62-5, 17627-44-0, 639-99-6, 107898-54-4, 65113-99-7, 8001-61-4, 68917-29-3, 87-44-5, 88-84-6, 489-84-9, 3691-12-1, 4630-07-3, 8006-87-9, 489-86-1, and 22451-73-6.

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internal toxicity thresholds, bioavailability, and chemical and biological activity, and considers the possible exposure of organisms in the aquatic and terrestrial environments on the basis of such factors as potential emission rates, overall persistence, and long-range transport potential in air. The various lines of evidence are combined to identify substances as warranting further evaluation of their potential to cause harm to the environment or as having a low likelihood of causing harm to the environment.

Some substances in the Phenylpropanoids and Aldehydes Group or the read-across analogues used in this assessment have been reviewed by the United States Environmental Protection Agency (US EPA), the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS), European Chemicals Agency (ECHA), European Food Safety Authority (EFSA), Joint FAO/WHO Expert Committee on Food Additives (JECFA), European Scientific Committee on Consumer Safety (SCCS), or the World Health Organization (WHO). Reviews conducted by these institutions have been used to inform the health effects characterization in this assessment.

Sabinene and phytol, which are main components of tarragon oil and jasmine oil, respectively, have been identified as possible ingredients in vaping products (US EPA 2019), which may represent an additional source of exposure to tarragon oil and jasmine oil. Vaping products (such as electronic cigarettes and vaping devices containing cannabis) are being addressed through separate legislative frameworks (HC [modified 2020]).

This draft assessment includes consideration of information on chemical properties, environmental fate, hazards, uses, and exposures, including additional information submitted by stakeholders. Relevant data were identified up to September 2020. Empirical data from key studies as well as some results from models were used to reach proposed conclusions.

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

Assessments focus on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by examining scientific information, including information, if available, on subpopulations who may have greater susceptibility or greater exposure, vulnerable environments and cumulative effects⁴, and by incorporating a weight-of-evidence approach and precaution.⁵ This draft assessment presents the critical information and considerations on which the proposed conclusions are based.

2. Identity of substances

The CAS RNs and *Domestic Substances List* (DSL) names for the discrete substances and representative substances for UVCBs (unknown or variable composition, complex reaction products, or biological materials) in the Phenylpropanoids and Aldehydes Group that were used to inform the human health assessments are presented in Tables 2-1 and 2-2, respectively. The substances in this assessment have been divided into two subgroups based on their chemical structure, properties, and/or toxicity, and three individual substances.

Terpenes are simple hydrocarbons consisting of repeating five-carbon isoprene units (Figure 2-1).

Terpenoids are a modified class of terpenes with different functional groups and oxidized methyl groups moved or removed at various positions. Both terpenes and terpenoids are classified according to the number of isoprene units they contain (Caputi and Aprea 2011; Perveen 2018). Monoterpenes contain two isoprene units. The prefixes di-, tri-, and tetra- refer to two, three, and four monoterpene units, respectively. Furthermore, sesquiterpenes and sesterpenes contain three and five isoprene units, respectively. Phenylpropanoids are characterized as having a chain of three carbon atoms attached to a benzene ring, and aldehydes contain the –CHO functional group and are considered as partially oxidized primary alcohols (Tisserand and Young 2014).

⁴ The consideration of cumulative effects under CEPA may involve an analysis, characterization and possible quantification of the combined risks to health or the environment from exposure to multiple chemicals.

⁵ 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.



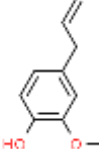
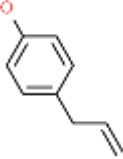
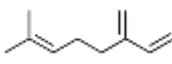
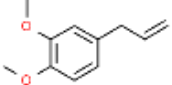
Figure 2-1. Isopropene unit

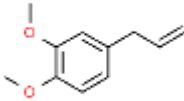
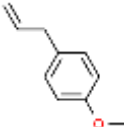

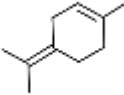
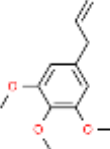
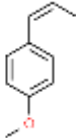
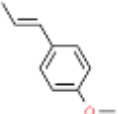
[The Figure 2-1 presents the structural formula of the isoprene (2-methyl-1,3-butadiene) molecule unit on the left (black) and the line (skeletal) formula on the right (blue). Both representations show a double bond between the first two carbons (C1 and C2) and a second double bond between the last two carbons (C3 and C4).]

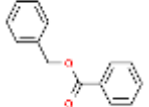
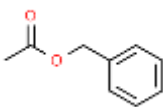
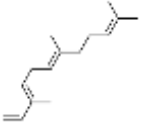
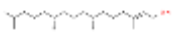
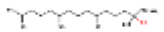

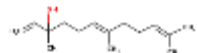
These substances are the components of essential oils found in a wide variety of plants. Essential oils are mixtures of volatile, organic compounds originating from a single botanical source and contribute to the flavour and fragrance of a plant. These plant-derived essential oils have many components that can be extracted from different parts of the plant (for example, leaves, seeds, stems, flowers, roots, fruits, woods, barks, grass, gum, tree blossoms, bulbs, and flower buds) (Tisserand and Young 2014). In addition, the concentration of these major components can be affected by different factors such as origin of the plant, species, temperature, soil, and geography. Essential

oils extracted from plants of the same genus and species can be chemically different even though their origin is the same.

Table 2-1. Substance identities for the Phenylpropanoids

Subgroup ^a	CAS RN	DSL name (common name)	Chemical structure or representative chemical name(s), structure(s), and their range of concentration(s) in the essential oil and molecular formula
Individual	8006-78-8	Oils, bay ^b (bay oil)	 <p>Eugenol 46–56%^c C₁₀H₁₂O₂</p>
			 <p>Chavicol 9–22%^d C₉H₁₀O</p>
			 <p>beta-Myrcene 13–26%^e C₁₀H₁₆</p>
			<p>Methyl eugenol 0–2%^f C₁₁H₁₄O</p> 

Subgroup ^a	CAS RN	DSL name (common name)	Chemical structure or representative chemical name(s), structure(s), and their range of concentration(s) in the essential oil and molecular formula
Individual	8016-88-4	Oils, tarragon ^b (tarragon oil)	<p>Methyl eugenol 2–39%^g C₁₁H₁₄O₂</p> 
			 <p>Estragole 0–82%^g C₁₀H₁₂O</p>
			<p>Sabinene Trace- 39%^h C₁₀H₁₆</p> 
			 <p>Terpinolene 0.5–25%ⁱ C₁₀H₁₆</p>
			 <p>Elemicin Trace-57%^j C₁₂H₁₆O₃</p>
			 <p>Cis- Anethole 51–81%^k C₁₀H₁₂O</p>
			<p>Trans- Anethole 21–53%^k C₁₀H₁₂O</p> 

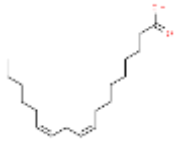

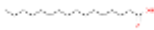

Subgroup ^a	CAS RN	DSL name (common name)	Chemical structure or representative chemical name(s), structure(s), and their range of concentration(s) in the essential oil and molecular formula
1	8022-96-6	Oils, jasmine ^b (Jasmine oil)	Benzyl benzoate 3–21% ^l $C_{14}H_{12}O_2$ 
			Benzyl acetate 0–31% ^m $C_6H_5CH_2O$ $COCH_3$ 
			(E,E)-alpha-Farnesene 1–26% ⁿ $C_{15}H_{24}$ 
			Phytol 11–26% ^o $C_{20}H_{40}O$ 
			Isophytol 5–12% ^p $C_{20}H_{40}O$ 
			Nerolidol Trace-13% ^q $C_{15}H_{26}O$ 
			Linalool 7–13% ^r $C_{10}H_{18}O$ 

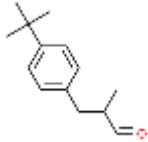
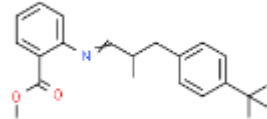
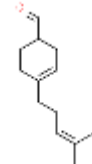
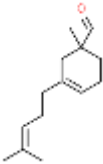
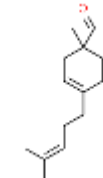
^l“Trace” is defined by less than 1%.

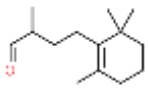
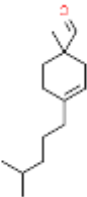
^aThe Phenylpropanoids Group was assessed under one subgroup and two individual substances. Phenylpropanoids subgroup 1 includes jasmine oil and perfumes and essences of jasmin due to their similar composition.

- ^b This substance is a UVCB. These materials are derived from natural sources or complex reactions and cannot be characterized in terms of constituent chemical compounds because their composition is too complex or variable. A UVCB is not an intentional mixture of discrete substances and is considered a single substance.
- ^c Concentration range of the main component(s) for *Pimenta racemosa* essential oil captured from Kim et al. (2008) and Bowles (2003).
- ^d Concentration range of the main component(s) for *Pimenta racemosa* essential oil captured from McHale et al. (1977), Tucker et al. (1991), Jirovetz et al. (2007a), and Kim et al. (2008).
- ^e Concentration range of the main component(s) for *Pimenta racemosa* essential oil captured from McHale et al. (1977), Tucker et al. (1991), Jirovetz et al. (2007a), and Kim et al. (2008).
- ^f Concentration range of the main component(s) for *Pimenta racemosa* essential oil captured from Tucker et al. (1991), Abaul et al. (1995), Kim et al. (2008), Jirovetz et al. (2007a).
- ^g Concentration range of the main component(s) for *Artemisia dracunculus* essential oil captured from Kordali et al. (2005), Lopes-Lutz et al. (2008), and Obolskiy et al. (2011).
- ^h Concentration range of the main component(s) for *Artemisia dracunculus* essential oil captured from Kordali et al. (2005) and Obolskiy et al. (2011).
- ⁱ Concentration range of the main component(s) for *Artemisia dracunculus* essential oil captured from Sayyah et al. (2004) and Obolskiy et al. (2011).
- ^j Concentration range of the main component(s) for *Artemisia dracunculus* essential oil captured from Obolskiy et al. (2011).
- ^k Concentration range of the main component(s) for *Artemisia dracunculus* essential oil captured from Ayoughi et al. (2011) and Obolskiy et al. (2011).
- ^l Concentration range of the main component(s) for *Jasminium grandiflorum* essential oil captured from Jirovetz et al. (2007b), Bera et al. (2015), Wei et al. (2015).
- ^m Concentration range of the main component(s) for *Jasminium grandiflorum* essential oil captured from Braun et al. (2009), Prakash et al. (2012), Bera et al. (2015), and Wei et al. (2015).
- ⁿ Concentration range of the main component(s) for *Jasminium grandiflorum* essential oil captured from Prakash et al. (2012) and Bera et al. (2015).
- ^o Concentration range of the main component(s) for *Jasminium grandiflorum* essential oil captured from Jirovetz et al. (2007b) and Wei et al. (2015).
- ^p Concentration range of the main component(s) for *Jasminium grandiflorum* essential oil captured from Tisserand and Young (2014), and Wei et al. (2015).
- ^q Concentration range of the main component(s) for *Jasminium grandiflorum* essential oil captured from Bera et al. (2015) and Wei et al. (2015).
- ^r Concentration range of the main component(s) for *Jasminium grandiflorum* essential oil captured from Prakash et al. (2012) and Bera et al. (2015).

Table 2-2. Substance identities for the Aldehydes Group

Subgroup ^a	CAS RN	DSL name (common name)	Chemical structure or representative chemical name(s), structure(s), and their range of concentration(s) in the essential oil and molecular formula
Individual	8024-08-6	Oils, violet ^b (violet oil)	<p>Linoleic acid 0–58%^c C₁₈H₃₂O₂</p> 
			 <p>2,6-Nonadienal 5–19%^c C₉H₁₄O</p>
			<p>Palmitic acid 0–17%^c C₁₆H₃₂HO₂</p> 
			 <p>1-Octadecene 0–11%^c C₁₈H₃₆</p>

Subgroup ^a	CAS RN	DSL name (common name)	Chemical structure or representative chemical name(s), structure(s), and their range of concentration(s) in the essential oil and molecular formula
2	80-54-6	Benzenepropanol, 4-(1,1-dimethylethyl)- α -methyl- (lilial)	 C ₁₄ H ₂₀ O
2	91-51-0	Benzoic acid, 2-[[[3-[4-(1,1-dimethylethyl)phenyl]-2-methylpropylidene]amino]-, methyl ester (verdantiol)	 C ₂₂ H ₂₇
2	37677-14-8	3-Cyclohexene-1-carboxaldehyde, 4-(4-methyl-3-pentenyl)- (myrac-aldehyde)	 C ₁₃ H ₂₀ O
2	52474-60-9	3-Cyclohexene-1-carboxaldehyde, 1-methyl-3-(4-methyl-3-pentenyl)- (myrmac-aldehyde)	 C ₁₄ H ₂₂ O
2	52475-86-2	3-Cyclohexene-1-carboxaldehyde, 1-methyl-4-(4-methyl-3-pentenyl)- (myrmac-carboxaldehyde)	 C ₁₄ H ₂₂ O

Subgroup ^a	CAS RN	DSL name (common name)	Chemical structure or representative chemical name(s), structure(s), and their range of concentration(s) in the essential oil and molecular formula
2	65405-84-7	Cyclohexenebutanal, α ,2,2,6-tetramethyl- (cetonal)	 <chem>CC(C)(C)CC=O</chem> $C_{14}H_{24}O$
2	66327-54-6	3-Cyclohexene-1-carboxaldehyde, 1-methyl-4-(4-methylpentyl)- (vernaldehyde)	 <chem>CC(C)CC(C)CC1=CC=CC=C1C=O</chem> $C_{14}H_{24}O$

^a The Aldehydes Group was assessed under one subgroup and one individual substance. Aldehydes subgroup 2 includes hazard information for linal used to inform the risk characterization. Linal is a discrete substance in aldehydes subgroup 2 and was identified as a read-across analogue for verdantol, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde. Verdantol seems to be an impurity and a possible metabolite of linal because verdantol can be hydrolyzed in linal.

^b This substance is a UVCB.

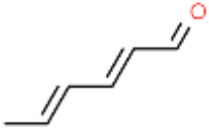
^c Concentration range of the main component(s) for *Viola odorata* captured from Cu et al. (1992) and Saint-Lary et al. (2014).

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

A read-across approach using data from analogues or components of the target substances, where appropriate, has been used to inform the human health assessments. Analogues were selected from among a large list of substances similar in structure and/or with characteristics similar to those of substances within this group (for example, in terms of physical-chemical properties, toxicokinetics). However, because the majority of the substances were data poor, the choice of analogues was driven by the presence of relevant empirical health effects data.

Selection was based on assessments carried out using the Organisation for Economic Co-operation and Development (OECD) (quantitative) structure-activity relationship [(Q)SAR] Toolbox version 4.3 (OECD 2019). Details of the read-across data chosen to inform the human health assessments of the phenylpropanoids and aldehydes are further discussed in the relevant sections of this assessment. Information on the identities and chemical structures of the analogues used to inform the human health assessment of the phenylpropanoids and aldehydes (that is, violet oil) is presented in Table 2.3.

Table 2-3. Identity of the analogue used in the human health risk assessment

Subgroup or substance being assessed	CAS RN for analogue	Common name	Chemical structure, molecular formula and SMILES	Molecular weight (g/mol)
Violet oil	142-83-6	2,4-Hexadienal	 C_6H_8O <chem>C\C=C\C=C\C=O</chem>	96.13

3. Physical and chemical properties

A summary of physical and chemical property data of the substances in the Phenylpropanoids and Aldehydes Group is presented in Table 3-1. Where experimental information was limited or not available for a property, data from analogues were used for read-across and/or (Q)SAR models (OECD 2019) were used to generate predicted values for the substance. Additional physical and chemical properties are reported in ECCC (2016b).

Table 3-1. Physical and chemical property values (at standard temperature) of the Phenylpropanoids and Aldehydes Group

Substance(s)	Common name (CAS RN) of representative constituent(s)	Molecular weight (g/mol) ^a	Water solubility (mg/L) ^a	Vapour pressure (Pa) ^a	Log K _{ow} ^a
Bay oil	Eugenol (97-53-0)	164.21	2460	1.26 ^(M)	2.27
Bay oil	Chavicol (501-92-8)	134.18	1110 ^(M)	3.04 ^(M)	2.91 ^(M)
Bay oil	beta-Myrcene (123-35-3)	136.24	5.6	268	4.17
Bay oil	Methyl eugenol (93-15-2)	178.23	500	4.46	3.03 ^(M)
Tarragon oil	Methyl eugenol (93-15-2)	178.23	500	4.46	3.03 ^(M)
Tarragon oil	Estragole (140-67-0)	148.21	178	22 ^(M)	3.47 ^(M)
Tarragon oil	Sabinene (3387-41-5)	136.24	2.49 ^(M)	981 ^(M)	4.69 ^(M)
Tarragon oil	Terpinolene (586-62-9)	136.24	9.5	99	4.47
Tarragon oil	Elemicin (487-11-6)	208.26	133.2 ^(M)	0.28 ^(M)	2.90 ^(M)
Tarragon oil	cis-Anethole (25679-28-1)	148.21	111	8.46 ^(M)	3.39 ^(M)
Tarragon oil	trans-Anethole (4180-23-8)	148.21	111	8.46 ^(M)	3.39 ^(M)
Jasmine oil	Benzyl acetate (140-11-4)	150.18	3100 ^(E)	23.6 ^(E)	1.96 ^(E)
Perfumes and essences of jasmin					
Jasmine oil	Benzyl benzoate (120-51-4)	212.25	15.39 ^(M)	0.03 ^(E)	3.97 ^(E)

Substance(s)	Common name (CAS RN) of representative constituent(s)	Molecular weight (g/mol) ^a	Water solubility (mg/L) ^a	Vapour pressure (Pa) ^a	Log K _{ow} ^a
Perfumes and essences of jasmin					
Jasmine oil	alpha-Farnesene (502-61-4)	204.36	1.05 x 10 ⁻² ^(M)	3.33 ^(M)	7.10 ^(M)
Perfumes and essences of jasmin					
Jasmine oil	Phytol (150-86-7)	296.54	3.27 x 10 ⁻³ ^(M)	4.30 x 10 ⁻⁴ ^(M)	8.32 ^(M)
Perfumes and essences of jasmin					
Jasmine oil	Isophytol (505-32-8)	296.54	7.53 x 10 ⁻³ ^(M)	1.88 x 10 ⁻³ ^(M)	8.23 ^(M)
Perfumes and essences of jasmin					
Jasmine oil	Nerolidol (7212-44-4)	222.37	7.67 ^(M)	0.08 ^(M)	5.68 ^(M)
Perfumes and essences of jasmin					
Jasmine oil	Linalool (78-70-6)	154.25	1590 ^(E)	21 ^(E)	2.9 ^(E)
Perfumes and essences of jasmin					
Violet oil	Linoleic acid (2197-37-7)	280.45	3.77 x 10 ⁻² ^(M)	1.16 x 10 ⁻⁴	7.05
Violet oil	2,6- Nonadienal (557-48-2)	138.21	318.8 ^(M)	31.1 ^(M)	2.84 ^(M)
Violet oil	Palmitic acid (57-10-3)	256.43	0.04	5.07 x 10 ⁻⁵	7.17
Violet oil	1-Octadecene (112-88-9)	252.48	1.26 x 10 ⁻⁴ ^(M)	8.99 x 10 ⁻³ ^(M)	9.04 ^(M)
Lilial	N/A	204.31	7.86 ^(M)	0.477 ^(M)	4.36 ^(M)
Verdantiol	N/A	337.46	0.028 ^(M)	4.0 x 10 ⁻⁵ ^(M)	6.35 ^(M)
Myrac-aldehyde	N/A	192.30	4.35 ^(M)	0.783 ^(M)	4.73 ^(M)
Myrmac-aldehyde	N/A	206.33	1.51 ^(M)	0.349 ^(M)	5.19 ^(M)
Myrmac-carboxaldehyde	N/A	206.33	1.51 ^(M)	0.349 ^(M)	5.19 ^(M)
Cetonal	N/A	208.35	1.44 ^(M)	0.834 ^(M)	5.20 ^(M)
Vernaldehyde	N/A	208.35	1.25 ^(M)	0.605 ^(M)	5.27 ^(M)

Abbreviations: N/A, not available; K_{ow}, octanol-water partition coefficient ; ^(M) Modelled; ^(E) Experienced

^a US EPA (2012a)

4. Sources and uses

All of the substances in the Phenylpropanoids and Aldehydes Group were included in a survey issued pursuant to a CEPA section 71 survey (Canada 2012). With the exception of lilial, none of the substances in this group were reported to be manufactured or imported into Canada in quantities greater than the reported threshold of 100 kg during the 2011 reporting year (Environment Canada 2013).

For lilial, 910 kg was reported to be manufactured in Canada in 2008, and 24 460 kg was reported to be imported into Canada during the same calendar year (Environment Canada 2013). Table 4-1 presents a summary of information submitted in response to a CEPA section 71 survey.

Table 4-1. Summary of information on Canadian manufacturing and imports of phenylpropanoids and aldehydes submitted in response to a CEPA section 71 survey

Substance	Total manufacture (kg) ^a	Total imports (kg) ^a	Reporting year
Bay oil	NR	NR	2011
Tarragon oil	NR	NR	2011
Jasmine oil	NR	NR	2011
Perfumes and essences of jasmin	NR	NR	2011
Violet oil	NR	NR	2011
Lilial	910	24 460	2008
Verdantiol	NR	NR	2011
Myrac-aldehyde	NR	NR	2011
Myrmac-aldehyde	NR	NR	2011
Myrmac-carboxaldehyde	NR	NR	2011
Cetonal	NR	NR	NA
Vernaldehyde	NR	NR	2011

Abbreviations: NR, no reports above the reporting threshold of 100 kg; NA, not applicable, and this substance was not included in the section 71 surveys

^a Values reflect quantities reported in response to a CEPA section 71 survey (Canada 2012). See surveys for specific inclusions and exclusions (Schedules 2 and 3).

Information submitted in response to a CEPA section 71 survey indicated uses of lilial as an odour agent in cleaning and furnishing care, laundry and dishwashing, personal care, air care, apparel and footwear care, pet care, automotive care, and in lubricants and greases (Environment Canada 2013). Information submitted in response to a CEPA section 71 survey also indicated uses of violet oil, myrac-aldehyde, and vernaldehyde in imported personal care products⁶ (Environment Canada 2013).

In addition, for myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde, an industry submission reported that these substances are used as a fragrance ingredient at low concentrations in cosmetics, air fresheners, and cleaning products.

Additional uses for the Phenylpropanoids and Aldehydes Group are outlined in Table 4-2.

⁶ Products used every day, available for purchase without a prescription. Personal care products fall into three broad categories: cosmetics, natural health products, or non-prescription drugs (Health Canada 2019c).

Table 4-2. Additional or potential uses in Canada for phenylpropanoids and aldehydes

Substance	Food flavouring agent ^a	Incidental additives ^{7,a}	Natural Health Products Ingredients Database	Licensed Natural Health Products Database ^b	Cosmetics ^c	Formulant PCPs ^d
Bay oil	Y	N	Y	Y (MI, NMI)	Y	Y
Tarragon oil	Y	N	Y	Y (MI, NMI)	Y	Y
Jasmine oil	Y	N	Y	Y (MI, NMI)	Y	N
Perfumes and essences of jasmin	N	N	Y	Y (MI, NMI)	N	N
Violet oil	Y	N	Y	Y (MI, NMI)	Y	N
Lilial	N	Y (Component in hand soaps, no direct food contact)	Y	Y (NMI)	Y	Y
Verdantiol	N	N	N	N	N	N
Myrac-aldehyde	N	N	N	N	N	Y
Myrmac-aldehyde	N	N	N	N	Y	Y
Myrmac-carboxaldehyde	N	N	N	N	N	N
Cetonal	N	N	N	N	N	N
Vernaldehyde	N	N	N	N	N	Y

Abbreviations: PCPs, pest control products; Y, yes, this use was reported for this substance; N, no, this use was not reported for this substance; MI, medicinal ingredient; NMI, non-medicinal ingredient

^a Personal communication, emails from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2015, 2017, and 2020; unreferenced.

^b Listed in the Licensed Natural Health Products Database as being present as a medicinal or non-medicinal ingredient in natural health products (NHPs) in Canada. Personal communication, email from the Natural and Non-prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2021; unreferenced.

^c Notified to be present in cosmetics based on notifications submitted under the *Cosmetic Regulations* to Health Canada. Personal communication, emails from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2017 and 2020; unreferenced.

^d Formulant in PCPs registered in Canada. Personal communication, emails from the Pest Management Regulatory Agency, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2015 and 2020; unreferenced.

Do-It-Yourself (DIY) Products

Certain terpene and terpenoid substances that have aromatic properties within the Phenylpropanoids and Aldehydes Group are currently available in the Canadian market (as “essential oils”) at a concentration of up to 100%. It is therefore possible that these undiluted substances are purchased and used by consumers to make DIY products. DIY products that may result in high consumer exposures include aromatic diffuser (known as aromatherapy by consumers), massage oil, bath oil product, body moisturizer, and facial steamer. Consequently, uses of undiluted substances in DIY

⁷ While not defined under the *Food and Drugs Act* (F&DA), incidental additives may be regarded, for administrative purposes, as those substances which are used in food processing plants and which may potentially become adventitious residues in foods.

products are evaluated in this assessment. Parameters for estimating dermal and inhalation exposures to DIY products are available in Appendix B.

Bay oil

Bay oil is a UVCB that is steam distilled from *Pimenta racemosa*, a tree that belongs to the *Myrtaceae* family. The tree is also known as the West Indian Bay tree, bay rum tree, and cilimnet; and while it is native to the Caribbean region, it is also cultivated in many warm parts of the world (Moharram et al. 2018). Stated otherwise, any extract from *Pimenta racemosa* to the *Myrtaceae* family is considered to be included in this definition.

Bay oil is used in a number of products available to consumers such as moisturizer, hair conditioner, bath product, and body cleanser. Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, bay oil⁸ is used in more than 90 products in Canada, with the majority (approximately 94%) having concentrations less than or equal to 3% (personal communication, emails from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced). There are also NHPs that contain bay oil as an MI (medicinal ingredient) or as an NMI (non-medicinal ingredient) acting as a fragrance ingredient (LNHPD [modified 2021]; personal communication, email communication from the Natural and Non-prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2021; unreferenced).

In Canada, bay oil is also reported to be used as a formulant in pest control products (PCPs) (personal communication, email from the Pest Management Regulatory Agency, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced).

Bay oil (myrcia oil) is listed as being generally recognized as safe (GRAS) under Title 21 Part 182 of the United States (US) *Code of Federal Regulations* (21CFR182.20). Bay leaves West Indian oil (*Pimenta acris* Kostel; *P. racemosa*) is listed as number 2122 in the Flavor and Extract Manufacturers Association (FEMA)'s Flavor Ingredient Library (FEMA 2020).

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

Bay oil has reported uses internationally as a flavouring agent in a variety of foods (CoE 2000; Burdock 2010). It does not have any specific food status in Europe; however, it is

⁸ Notifications submitted under the *Cosmetic Regulations* to Health Canada were for products containing bay oil, laurel (*Laurus nobilis*) oil, *Laurus nobilis* (bay laurel) leaf oil, *Laurus nobilis* (bay) oil, *Pimenta acris* (bay) leaf oil, and *Pimenta racemosa* (bay) leaf oil.

listed in the United States Food and Drug Administration (US FDA) Substances Added to Food Inventory as a flavouring agent or adjuvant (EC 2008; US FDA 2018). No definitive information is available concerning the potential use of bay oil as a food flavouring agent in Canada; however, since the substance is identified as a food flavouring agent internationally, it is possible that the substance is present as a flavouring agent in foods sold in Canada (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced).

Tarragon oil

Tarragon oil is a UVCB that is steam distilled from *Artemisia dracunculus*, a plant that belongs to the *Asteraceae* family. The plant has various common names such as estragon, dragon sage-wort, false tarragon, and dragon wormwood. It is cultivated in many countries, including Iran (Raeisi et al. 2012). Unless explicitly specified, any extract from *Artemisia dracunculus* to the *Asteraceae* family is considered to be included in this definition.

Tarragon oil is used in some products available to consumers such as moisturizer, fragrances, massage oil, and antiperspirant/deodorant. Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, tarragon oil or *Artemisia dracunculus* (tarragon) oil is used in approximately 30 products, with the majority (approximately 80%) having concentrations less than or equal to 3% (personal communication, email from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada 2020; unreferenced). There are also NHPs that contain tarragon oil as an MI, or as an NMI for the purpose of flavour enhancer, fragrance ingredient, or skin-conditioning agent (LNHPD 2021; personal communication, email communication from the Natural and Non-prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2021; unreferenced).

In Canada, tarragon oil is also reported to be used as a formulant in PCPs (personal communication, email from the Pest Management Regulatory Agency, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced).

Estragole (esdragol, esdragon, tarragon), estragon (tarragon), and tarragon are listed as being GRAS under Title 21 Part 182 of the US 21CFR182.20. Tarragon (*Artemisia dracunculus* L.) is listed as number 3043 in the FEMA's Flavor Ingredient Library (FEMA 2020). Estragon oil (*Artemisia dracunculus* L.; tarragon oil) is listed with FEMA number 2412 (FEMA 2020).

Annex III to Regulation (EC) No 1334/2008 sets out substances which should not be added to food, and maximum levels (MLs) for certain substances in the European Union (EU), which are naturally present in flavourings and in food ingredients with flavouring properties. The MLs must not be exceeded as a result of the use of flavourings and/or

food ingredients with flavouring properties in and on those foods in the EU. Annex III prohibits the addition of estragole to foods, as such, and sets out the MLs for estragole in certain compound foods⁹ resulting from its natural presence in flavourings and/or food ingredients with flavouring properties used in the foods. Tarragon oil is composed of approximately 0% to 82% estragole, and the amount of estragole in foods from the use of tarragon oil or other flavouring preparations would be subject to the MLs in Regulation (EC) No 1334/2008 in the EU.

Tarragon oil is identified by IFRA (2017) as a fragrance ingredient used in consumer goods.

Tarragon oil has reported uses internationally as a flavouring agent in a variety of foods (CoE 2000; Burdock 2010). Tarragon oil does not have any specific food status in Europe; however, it is listed in the US FDA Substances Added to Food Inventory as a flavouring agent or adjuvant (EC 2008; US FDA 2018). No definitive information is available concerning the potential use of tarragon oil as a food flavouring agent in Canada; however, since the substance is identified as a food flavouring agent internationally, it is possible that the substance is present as a flavouring agent in foods sold in Canada (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced).

Furthermore, sabinene, one of the main components of tarragon oil, has been identified in vaping products in the United States (US EPA 2019).

Phenylpropanoids subgroup 1 (jasmine oil, perfumes and essences of jasmin)

There are two UVCBs in phenylpropanoids subgroup 1: jasmine oil, and perfumes and essences of jasmin. Both substances are produced from the fresh flowers of several jasmine species (*Jasminum* spp.) of the *Oleaceae* family. There are more than 2000 known species of jasmine. The most common species are *Jasminum officinale*, *J. grandiflorum*, *J. floribundum*, *J. humile*, *J. odoratissimum*, *J. paniculatum*, and *J. sambac*. Jasmine varieties originate from India but are also well known in the Mediterranean countries of Europe, Asia, and Africa, the Comoro Islands, and China. The major suppliers of aromatic products obtained from jasmine are Egypt, Morocco, Algeria, Italy, and France (Jirovetz et al. 2007b). Unless explicitly specified, any extract from *Jasminum* spp. to the *Oleaceae* family is considered to be included in this definition.

⁹ MLs have been established in the EU for estragole added via flavouring preparations and/or food ingredients with flavouring properties in dairy products (50 mg/kg); processed fruits, processed vegetables (including mushrooms, fungi, roots, tubers, pulses and legumes), and processed nuts and seeds (50 mg/kg); fish products (50 mg/kg); and non-alcoholic beverages (10 mg/kg), as consumed (EC 2008).

Jasmine oil and perfumes and essences of jasmin have been identified by two different CAS RNs; however, the *Toxic Substances Control Act* Chemical Substance Inventory defines both as “extractives and their physically modified derivatives from *Jasminum officinale*, *Oleaceae*” (ChemIDPlus 2019). They also share similar synonyms, such as jasmine absolute or jasmin (ChemIDPlus 2019). IFRA identified both CAS RNs as identical substances (IFRA 2013). Therefore, jasmine oil and perfumes and essences of jasmin are assessed herein as the same substance. IFRA also identified CAS RN 90045-94-6, named *Jasmin officinale* var. *grandiflorum*, as being identical to jasmine oil and perfumes and essences of jasmin (IFRA 2013). The two substances will be referred to as jasmine oil.

Jasmine oil is in a number of products available to consumers such as body moisturizer, body fragrance, massage oil, makeup, and facial cleaners. Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, jasmine oil¹⁰ is used in approximately 550 products in Canada, with the majority (approximately 78%) having concentrations of less than or equal to 1% (personal communication, email from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced). There are also NHPs that contain jasmine oil as an MI or as an NMI acting as a fragrance ingredient or skin-conditioning agent (LNHPD 2021; personal communication, email communication from the Natural and Non-prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2021; unreferenced).

Jasmine oil may be present in cleaning products, such as liquid or gel all-purpose cleaners in pourable bottles, pump sprays or aerosols at concentrations up to 1%, liquid or gel dish detergents in pourable bottles for washing by hand or by automatic dishwashing machines at concentrations up to 1%, liquid laundry conditioners available in pourable bottles for use in washing machines or applied directly to fabric as a spray or aerosol at concentrations up to 5%, and liquid laundry detergent and detergent boosters available in pourable bottles for use in a washing machine at concentrations up to 5% (ACI 2020). Jasmine oil is also present in fragrance oil burners (MSDS 2006).

Essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of jasmine (*Jasminum officinale* L. and other *Jasminum* spp.) are listed as being GRAS under Title 21 Part 182 of the US 21CFR182.20.

¹⁰ Notifications submitted under the *Cosmetic Regulations* to Health Canada were for products containing jasmine, jasmine absolute, jasmine oil, *Jasminum officinale* (jasmine) oil, *Jasminum grandiflorum* (jasmine) flowers, and *Jasminum grandiflorum* oil.

Jasmine oil (*Jasminium grandiflorum* L.) is listed as number 2600 in the FEMA's Flavor Ingredient Library (FEMA 2020).

Jasmine oil is identified by IFRA (2017) as a fragrance ingredient used in consumer goods.

Jasmine oil has reported uses internationally as a flavouring agent in a variety of foods (CoE 2000; Burdock 2010). Jasmine oil does not have any specific food status in Europe; however, it is listed in the US FDA Substances Added to Food Inventory as a flavouring agent or adjuvant (EC 2008; US FDA 2018). No definitive information is available concerning the potential use of jasmine oil as a food flavouring agent in Canada; however, since the substance is identified to be used as a food flavouring agent internationally, it is possible that the substance is present as a flavouring agent in foods sold in Canada. There is no information available to indicate that perfumes and essences of jasmin have any direct or indirect food uses in Canada or internationally (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced).

Furthermore, phytol, one of the main components of jasmine oil, has been identified in vaping products in the United States (US EPA 2019).

Violet oil

Violet oil is a UVCB obtained from *Viola odorata*, a plant that belongs to the *Violaceae* family. The plant is native to Asia, North Africa, and Europe. Unless explicitly specified, any extract from *Viola odorata* is considered to be included in this definition.

Violet oil is used in a number of products available to consumers such as body moisturizer, fragrances, facial cleanser, styling products, and lipstick. Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, violet oil¹¹ is used in more than 400 products, with the majority (90%) having a concentration less than or equal to 1% (personal communication, email from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, March 2017; unreferenced). There are also NHPs that contain violet oil as an MI, or as an NMI acting as a fragrance ingredient (LNHPD 2021; personal communication, email from the Natural and Non-prescription Health Products

¹¹ Notifications submitted under the *Cosmetic Regulations* to Health Canada were for products containing hydrolyzed *Viola tricolour* extract, sorbitol *Viola odorata* extract, *Viola adunca* flower, *Viola glabella* flower, *Viola mandshurica* flower extract, *Viola odorata* (violet) oil, *Viola odorata* extract, *Viola odorata* flower extract, *Viola odorata* flower/leaf extract, *Viola odorata* leaf extract, *Viola odorata* leaf wax, *Viola tricolour* extract, *Viola yedoensis* extract, African violet, parfum de violette, *Viola odorata* flower/leaf extract (notified as sweet violet extract), *Viola odorata* oil (notified as sweet violet extract), violet extract, and violet flowers.

Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2021; unreferenced).

Essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of the violet flowers, leaves, and leaves absolute are listed as being generally recognized as safe (GRAS) under Title 21 Part 182 of the US' 21CFR182.20. Violet leaves absolute (*Viola odorata* L.) is listed with the number 3110 in the FEMA's Flavor Ingredient Library (FEMA 2020).

Violet oil is identified by IFRA (2017) as a fragrance ingredient used in consumer goods.

Violet oil has reported uses internationally as a flavouring agent in a variety of foods (Burdock 2010; CoE 2000). Violet oil does not have any specific food status in Europe; however, it is listed in the US FDA Substances Added to Food Inventory as a flavouring agent or adjuvant (EC 2008; US FDA 2018). No definitive information is available concerning the potential use of violet oil as a food flavouring agent in Canada; however, since the substance is identified as a food flavouring agent internationally, it is possible that the substance is present as a flavouring agent in foods sold in Canada (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced).

Aldehydes subgroup 2 (lilial, verdantiol, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, vernaldehyde)

There are seven discrete substances in aldehydes subgroup 2 (lilial, verdantiol, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde).

Lilial is used in a number of products available to consumers such as body moisturizer, massage oil, fragrances, hair conditioners, hair colouring products, and nail polish. Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, lilial is used in approximately 6500 products, with the majority (90%) having concentrations less than or equal to 0.3% (personal communication, email from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, 2020; unreferenced). There are also NHPs that contain lilial as an NMI acting as a fragrance ingredient, in addition to non-prescription drugs such as sunscreens and makeup products with sun protection (LNHPD 2021; personal communication, email from the Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced; personal communication, email from the Natural and Non-prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2021; unreferenced).

In Canada, lilial, myrac-aldehyde, myrmac-aldehyde, and vernaldehyde were also reported to be used as formulants in PCPs (personal communication, email from the Pest Management Regulatory Agency, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced).

In addition, lilial may be present in cleaning products (ACI 2020). Lilial is also present in air fresheners and carpet deodorizer (SDS 2016, 2017a, 2017b). Myrac-aldehyde, myrmac-aldehyde, and myrmac-carboxaldehyde are also used in air fresheners (CPID 2021 ~~2019~~).

Lilial is used as a component in incidental additives (for example, hand soaps) used in food processing establishments with no direct food contact (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced). There is no information available to indicate that any of the other aldehydes subgroup 2 substances have any direct or indirect food uses in Canada or internationally (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced).

Lilial, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde are primarily used as fragrance ingredients in products available to consumers in Canada and are typically present as part of fragrance mixtures at low concentrations (Environment Canada 2013).

An industry submission indicated that the substances in aldehydes subgroup 2 are used as fragrance ingredients at low concentrations and can be present in certain product categories such as cosmetics, air fresheners, and cleaning products.

5. Environmental fate and behaviour

5.1 Environmental persistence

According to models used in ERC, lilial and perfumes and essences of jasmin are expected to persist in water, sediment, and soil but are not expected to persist in air (ECCC 2016b).

According to models used in ERC, violet oil, myrmac-carboxaldehyde, and vernaldehyde are expected to persist in sediment but are not expected to persist in water, soil, or air (ECCC 2016b).

According to models used in ERC, jasmine oil is expected to persist in air but is not expected to persist in water, sediment, or soil (ECCC 2016b).

According to models used in ERC, bay oil, tarragon oil, verdantiol, myrac-aldehyde, myrmac-aldehyde, and cetonal are not expected to persist in air, water, sediment, or soil (ECCC 2016b).

5.2 Potential for bioaccumulation

Although the log K_{ow} values for verdantiol, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde are moderate to high, the bioconcentration factors for these substances are low. As a result, verdantiol, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde are not expected to significantly bioaccumulate in organisms (ECCC 2016b).

Given their low K_{ow} and low bioconcentration factors, bay oil, tarragon oil, jasmine oil, perfumes and essences of jasmin, violet oil, lilial, and myrac-aldehyde are not expected to significantly bioaccumulate in organisms (ECCC 2016b).

6. Potential to cause ecological harm

6.1 Characterization of ecological risk

The ecological risks of the substances in the Phenylpropanoids and Aldehydes Group were characterized using the 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 associated with risk characterization compared to an approach that relies on a single metric in a single medium (for example, median lethal concentration) for characterization. Since violet oil is a UVCB substance and could not be suitably represented by a single chemical structure, a manual judgement-based approach to classification was used. The following summarizes the approach, which is described in detail in ECCC (2016a).

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

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

exposure. However, in the case of violet oil, hazard and exposure could not be fully profiled because of the lack of a representative structure to estimate needed properties and the lack of empirical data for these properties. Therefore, classification of hazard and exposure was performed manually by examining the UVCB constituents, analyzing information submitted in response to a CEPA section 71 survey, and making decisions on the basis of consideration of similar substances and/or application of expert judgement.

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

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

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

The hazard and exposure classifications for the 12 substances in the Phenylpropanoids and Aldehydes Group are summarized in Table 6-1.

Table 6-1. ERC results for the substances in the Phenylpropanoids and Aldehydes Group

Substance	ERC hazard classification	ERC exposure classification	ERC risk classification
Bay oil	low	low	low
Tarragon oil	low	low	low
Jasmine oil	low	high	low
Perfumes and essences of jasmin	low	low	low
Violet oil	low	low	low
Lilial	low	low	low
Verdantiol	low	low	low
Myrac-aldehyde	low	low	low
Myrmac-aldehyde	low	low	low
Myrmac-carboxaldehyde	low	low	low
Cetonal	low	low	low
Vernaldehyde	low	low	low

On the basis of the low hazard and low exposure classifications according to information considered under the ERC, bay oil, tarragon oil, perfumes and essences of jasmin, violet oil, lilial, verdantiol, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde were classified as having a low potential for ecological risk. It is unlikely that these substances are resulting in concerns for the environment in Canada.

According to information considered under the ERC, jasmine oil was classified as having a high exposure potential on the basis of its critically long half-life in air. Although the current use patterns for jasmine oil result in a high exposure potential, considering its low hazard potential, jasmine oil is unlikely to be resulting in concerns for the environment in Canada.

7. Potential to cause harm to human health

For the health effects characterization of the substances in the Phenylpropanoids and Aldehydes Group, preference was given to hazard data on the oil itself. In the absence of health effects data on the oil, health effects data for the major components present in the oil of interest were considered in order to inform the risk assessment. Where there were no health effects data for the substance and/or major components in the oil, a read-across approach was taken.

Certain subpopulations have the potential for increased exposure due to differences in physical characteristics (for example, body weight, breathing rate, skin surface area). As a result of potential differences in exposure, these vulnerable populations may be at increased risk of experiencing adverse health effects. In this assessment, exposure

estimates were derived for infants, toddlers, and children, who may have higher exposures per kilogram (kg) body weight (bw) than adults for certain products available to consumers, such as body lotions, sunscreens, and hand sanitizers. Additionally, where available and appropriate, reproductive and developmental studies were considered to ensure that pregnant women and their developing fetuses are protected.

7.1 Bay oil

7.1.1 Exposure assessment

Environmental media

No uses for bay oil were indicated in the information submitted in response to a CEPA section 71 survey. Monitoring data for bay oil in environmental media in Canada or elsewhere were not identified. According to information considered under the ERC, bay oil was classified as having a low ecological exposure potential (see section 6.1).

Food

No definitive information is available concerning the potential use of bay oil as a flavouring agent in foods sold in Canada. However, since bay oil is identified as a food flavouring agent internationally, it is possible that this substance is present as a flavouring agent in foods sold in Canada.

The Fenaroli's Handbook of Flavour Ingredients reports the per capita ("individual") estimated intake of bay oil from its use as a food flavouring agent to be 3.39×10^{-1} µg/kg bw/day on the basis of a maximized survey-derived daily intake (MSDI) approach for the US population (Burdock 2010). In the absence of data on the actual use, if any, of bay oil as a flavouring agent in foods sold in Canada, the per capita intake estimate for the US population (Burdock 2010) is an acceptable estimate of possible Canadian dietary exposure for the general population 1 year of age and older to this substance from its potential use as a food flavouring agent (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced).

Exposure from natural occurrence in foods

No definitive information is available concerning the natural occurrence of bay oil in foods. However, limited dietary exposure, if any, is expected to this substance from its natural presence in foods (Nijssen et al. 2018).

Products available to consumers

Depending on the source, bay oil may contain methyl eugenol at concentrations of 0% to 2%. In cosmetics in Canada, methyl eugenol is described as a restricted ingredient on the Cosmetic Ingredient Hotlist.¹² The Cosmetic Ingredient Hotlist describes methyl eugenol as only permitted as a naturally occurring component in botanical extracts 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 products and oral hygiene products, and 0.001% in rinse-off products (HC 2019a).

Bay oil is present in products available to consumers. To evaluate the potential exposure to bay oil from cosmetics and NHPs applied by the dermal and inhalation routes, sentinel scenarios were selected based on a combination of use frequencies and reported concentrations of bay oil in these products. The selected sentinel scenarios below represent the highest exposures, relative to other cosmetics and age groups as well as NHPs where bay oil is used as an NMI, based on identified products reported to contain this substance. Given the presence of methyl eugenol on the Cosmetic Ingredient Hotlist as being restricted in such products, it has been assumed that conditions indicated on the Cosmetic Ingredient Hotlist are met and that the exposures to bay oil are based on assuming the maximum permitted methyl eugenol Cosmetic Ingredient Hotlist concentrations in each product.

The use of 100% bay oil in DIY products such as aromatic diffuser, massage oil, bath oil product, and body moisturizer were assessed. Although the upper concentration reported for massage oil containing bay oil was 100%, massage oils are typically diluted prior to use. Therefore, the maximum concentration of bay oil in DIY massage oil was assumed to be 3% (RIVM 2006). It is reported that body products are typically diluted to concentrations of 1% to 4% (Tisserand Institute 2021). Based on this information, the maximum concentration of bay oil in DIY body moisturizer was assumed to be 3%.

In the absence of any chemical-specific dermal absorption data, a dermal absorption value of 40% for methyl eugenol was used to estimate systemic exposure from dermal exposure (EC, HC 2010). To account for the amount of product absorbed by the dermal route, the product amount available for inhalation was adjusted by 60%, except for body moisturizer. For body moisturizer, since the product amount for inhalation was adjusted for the exposed surface area, and since this value was less than 60% of the product amount, no further adjustment was made to the product amount.

¹² The List of Prohibited and Restricted Cosmetic Ingredients (more commonly referred to as the Cosmetic Ingredient Hotlist or simply the Hotlist) is an administrative tool that Health Canada uses to communicate to manufacturers and others that certain substances, when present in a cosmetic, may contravene the general prohibition found in section 16 of the F&DA) or a provision of the *Cosmetic Regulations*. Section 16 of the F&DA states that “No person shall sell any cosmetic that has in or on it any substance that may cause injury to the health of the user.” In addition, the Hotlist includes certain substances that may make it unlikely for a product to be classified as a cosmetic under the F&DA (Health Canada [modified 2019a]).

Lowest and highest systemic (sum of inhalation and dermal) daily exposure estimates as well as calculated lifetime average daily doses (LADDs) of methyl eugenol in bay oil from cosmetics and NHPs are summarized in Tables 7-1 and 7-2, respectively. Lowest and highest systemic daily exposure estimates and LADDs of methyl eugenol from DIY products containing bay oil are summarized in Table 7-3.

Table 7-1. Estimated daily and lifetime amortized exposures to methyl eugenol from cosmetics containing bay oil

Product scenario	% of methyl eugenol in product	Systemic daily exposure ^a (mg/kg bw/day)	LADD ^b (mg/kg bw/day)
Fine fragrance (spray)	0.01%	2.66 x 10 ⁻⁴ (14–18 years) to 4.15 x 10 ⁻⁴ (4–8 years)	2.94 x 10 ⁻⁴
Eau de toilette	0.004%	1.24 x 10 ⁻⁴ (14–18 years) to 1.90 x 10 ⁻⁴ (4–8 years)	1.31 x 10 ⁻⁴
Fragrance cream	0.002%	1.06 x 10 ⁻³ (14-18 years) to 2.05 x 10 ⁻³ (0-5 months)	1.17 x 10 ⁻³
Hair conditioner (leave-on)	0.0002%	1.39 x 10 ⁻⁵ (14–18 years) to 2.34 x 10 ⁻⁵ (adults)	2.12 x 10 ⁻⁵
Body cleanser	0.001%	9.35 x 10 ⁻⁶ (adults) to 3.47 x 10 ⁻⁵ (0–5 months)	1.08 x 10 ⁻⁵

^a Only lowest to highest exposed age groups are presented. Exposure estimates for bay oil have been adjusted assuming that methyl eugenol is present at the maximum permitted concentrations indicated on the Hotlist.

^b LADD = Lifetime average daily dose; see Appendix A for calculation details.

Table 7-2. Estimated daily and lifetime amortized exposures to methyl eugenol from NHPs containing bay oil

Product scenario	% of bay oil in product	Systemic daily exposure ^a (mg/kg bw/day)	LADD ^b (mg/kg bw/day)
Inhaler stick	0.06%	1.33 x 10 ⁻⁵ (adults)	1.01 x 10 ⁻⁵
Respiratory air spray	2%	8.48 x 10 ⁻⁶ (adults)	6.41 x 10 ⁻⁶

^a Only lowest to highest exposed age groups are presented. Exposure estimates for bay oil have been adjusted for a maximum concentration of 2% methyl eugenol.

^b LADD = Lifetime average daily dose; see Appendix A for calculation details.

Table 7-3. Estimated daily and lifetime amortized exposures to methyl eugenol from DIY products containing bay oil

Product scenario	% of bay oil in the final product	Systemic daily exposure ^a (mg/kg bw/day)	LADD ^b (mg/kg bw/day)
Aroma diffuser	100%	2.07 x 10 ⁻² (adults) to 3.93 x 10 ⁻² (1 year)	2.3 x 10 ⁻²
Massage oil	3%	1.25 x 10 ⁻³ (adults) to 9.13 x 10 ⁻³ (0–5 months)	1.37 x 10 ⁻²
Bath oil product	100%	8.37 x 10 ⁻⁴ (adults) to 1.35 x 10 ⁻⁵ (9–13 years)	7.87 x 10 ⁻⁴
Body moisturizer	3%	3.18 x 10 ⁻² (adults) to 6.13 x 10 ⁻² (0–6 months)	3.5 x 10 ⁻²

^a Only lowest to highest exposed age groups are presented. Exposure estimates for bay oil have been adjusted for a maximum concentration of 2% methyl eugenol.

^b LADD = Lifetime average daily dose; see Appendix B for calculation details.

7.1.2 Health effects assessment

There are no empirical health effects data available and no international assessments for bay oil.

In order to inform the health effects assessment, the hazard information available for the main components of bay oil, eugenol (46%–56%), chavicol (9%–22%), beta-myrcene (13%–26%), and methyl eugenol (0%–2%) was considered.

Eugenol was considered to be a substance of low hazard potential; therefore, the risk for human health from exposure to eugenol was considered to be low by ECCC and HC in a screening assessment (ECCC, HC 2018d).

There are no empirical health effects data available and no international assessments for chavicol.

The International Agency for Research on Cancer (IARC) considers beta-myrcene as a medium priority agent to be evaluated and classifies it in group 2B: possibly carcinogenic to humans (IARC 2014). The Office of Environmental Health Hazard Assessment (OEHHA) in California is adding Beta-Myrcene to the list of chemicals known to the state to cause cancer in laboratory animals for purposes of Proposition 65 (OEHHA 2018). Beta-myrcene is also not considered genotoxic (IARC 2014; US FDA 2018; OEHHA 2018; ECCC, HC 2020). A no-observed-adverse-effects level (NOAEL) of 250 mg/kg bw/day beta-myrcene was determined for reproductive and developmental toxicity based on a decrease in the number of implantation sites of live fetuses and an

increase in the frequency of skeletal malformations as fused zygomatic, dislocated sternum, and lumbar extra ribs at 500 mg/kg bw/day in rats by ECCC and HC (2020).

The US National Toxicology Program (NTP) has classified methyl eugenol as reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals (NTP 2000). The IARC also evaluated methyl eugenol and concluded that there is sufficient evidence from experimental animals for its carcinogenicity (IARC 2013). The IARC therefore classified methyl eugenol as possibly carcinogenic to humans (group 2B) (IARC 2013).

Consistent with the NTP 2-year bioassay in 2005, the Government of Canada has concluded that methyl eugenol is genotoxic and carcinogenic and determined a lowest-observed-adverse-effects level (LOAEL) of 37 mg/kg bw/day, the lowest dose tested, based on the presence of liver and glandular stomach tumours in both rats and mice in both sexes (NTP 2000; EC, HC 2010).

For methyl eugenol, there is no published benchmark dose (BMD) value derived by an international agency. However, there are several BMD values available in the scientific literature based on the same standard 2-year NTP carcinogenic study (2000) and used by the Government of Canada to assess the risk of methyl eugenol (EC, HC 2010).

In a first genotoxicity and carcinogenic evaluation study of compounds that can be found in food and plant-based supplements, BMDL₁₀ range values were obtained with the US EPA BMDS software version 2.1.2 using different models, including the Gamma, Logistic, Log-logistic, Probit, Log-probit, Multistage, Weibull, and Quantal linear model. BMD software was applied using default settings for model restrictions, risk type (extra), confidence level (95%), and basal metabolic rate (10%). Dose-response data for induction of hepatocellular carcinoma in male and female F344/N rats was calculated and adjusted for the duration of exposure (5 days instead of 7 days per week dosing regimen) (Van den Berg et al. 2011). For methyl eugenol, BMD₁₀ values of 15.3 mg/kg bw/day to 34 mg/kg bw/day were determined for male rats and values of 48.8 mg/kg bw/day to 73.6 mg/kg bw/day were determined for female rats (Van den Berg et al. 2011).

In a second risk assessment study, the authors estimated BMDs to determine the MOEs in different herbal beverages (Suparmi et al. 2019). To determine the BMDL₁₀, the dose-response data for induction of hepatocellular carcinoma in male and female F344/N rats were calculated and adjusted with the time of exposure (5 days instead of 7 days per week dosing regimen) (Suparmi et al. 2019). BMDL₁₀ values were obtained by following EFSA Scientific Committee recommendations through averaging model results rather than selecting or rejecting a specific model (EFSA 2017). The approach also used EFSA's tool for BMD analysis, which implements statistical methods for R-package PROAST. BMDL₁₀ model averaging was performed using the default settings. The BMD₁₀ value for male rats was determined to be 22.2 mg/kg bw/day and 66.5 mg/kg bw/day for female rats (Suparmi et al. 2019). Both values land in the range of BMD₁₀ values determined in the previous study.

Other studies were also considered but did not follow US EPA or EFSA guidelines for cancer analysis (Rietjens et al. 2008; Smith et al. 2010).

In general, the mouse was observed to be the most sensitive species and resulted in the lowest observed doses for tumour endpoints. However, the modelling of the mouse data was found to be problematic due to the absence of a dose-response trend; as a result, data could not be fitted well to any statistical model. Because of these difficulties with the mouse data, many authors have selected dose-response data based on hepatic adenomas in male rats to derive a BMD for methyl eugenol (Rietjens et al. 2008; Smith et al. 2010; Van den Berg et al. 2011; Suparmi et al. 2019).

7.1.3 Characterization of risk to human health

The identified endpoint of concern for bay oil is genotoxic carcinogenicity for methyl eugenol with a BMDL₁₀ of 22.2 mg/kg bw/day based on a significantly increased incidence of hepatocellular carcinoma in male rats in a dose-related manner in a 2-year NTP carcinogenicity study (2000) (Suparmi et al. 2019). To determine the risk from bay oil containing methyl eugenol, MOEs were determined by comparing the estimated LADDs resulting from product use to the BMDL₁₀ for methyl eugenol.

LADDs and resulting MOEs for methyl eugenol in bay oil from cosmetics containing bay oil are summarized in Table 7-4, while those from food and NHPs are summarized in Table 7-5. LADDs and MOEs from DIY products containing bay oil are summarized in Table 7-6.

Table 7-4. LADDs and resulting MOEs of methyl eugenol from bay oil in cosmetics

Exposure scenario	LADD^a (mg/kg bw/day)	MOE^b
Systemic exposure by the dermal and inhalation routes from fine fragrance (0.01%)	2.94 x 10 ⁻⁴	>75 000
Systemic exposure by the dermal and inhalation routes from eau de toilette (0.004%)	1.31 x 10 ⁻⁴	>169 000
Systemic exposure by the inhalation route from fragrance cream (0.002%)	1.17 x 10 ⁻³	>19 000
Systemic exposure by the dermal and inhalation routes from hair conditioner (leave-on) (0.0002%)	2.12 x 10 ⁻⁵	>1 000 000

Systemic exposure by the dermal and inhalation routes from body cleanser (0.001%)	1.08×10^{-5}	>2 000 000
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^a The LADDs were adjusted assuming the maximum Cosmetic Ingredient Hotlist concentrations of methyl eugenol.

^b The MOEs were calculated using a BMDL₁₀ of 22.2 mg/kg bw/day based on the carcinogenicity of methyl eugenol.

Table 7-5. LADDs and resulting MOEs of methyl eugenol from bay oil in food and NHPs

Exposure scenario	LADD ^a (mg/kg bw/day)	MOE ^b
Food flavouring agent (1 year of age and older)	6.78×10^{-6}	>3 000 000
Systemic exposure by the inhalation route from an inhaler stick (0.06%)	1.01×10^{-5}	>2 000 000
Systemic exposure by the inhalation route from a respiratory air spray (2%)	6.41×10^{-6}	>3 000 000

^a For bay oil as a food flavouring agent, as well as in inhaler stick and respiratory air spray, the LADDs were adjusted for a maximum concentration of 2% methyl eugenol.

^b The MOEs were calculated using a BMDL₁₀ of 22.2 mg/kg bw/day based on the carcinogenicity of methyl eugenol.

Table 7-6. LADDs and resulting MOEs of methyl eugenol from bay oil in DIY products

Exposure scenario	LADD ^a (mg/kg bw/day)	MOE ^b
Systemic exposure by the dermal and inhalation routes from DIY aromatic diffuser (100%)	2.3×10^{-2}	965
Systemic exposure by the dermal and inhalation routes from DIY massage oil (3%)	1.6×10^{-3}	13 891
Systemic exposure by the dermal and inhalation routes from a DIY bath oil product (100%)	7.88×10^{-4}	28 000
Systemic exposure by the dermal and inhalation routes from DIY body moisturizer (3%)	3.5×10^{-2}	633

^a For bay oil in aromatic diffuser, massage oil, bath oil product, and body moisturizer, the LADDs were adjusted for a maximum concentration of 2% methyl eugenol.

^b The MOEs were calculated using a BMDL₁₀ of 22.2 mg/kg bw/day based on the carcinogenicity of methyl eugenol.

The MOEs for bay oil from cosmetics, food flavouring agent, inhaler stick, and respiratory air spray (NHPs) are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk.

The MOEs for bay oil from a DIY bath oil and a DIY massage oil are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk.

For exposures to bay oil in DIY aromatic diffuser and DIY body moisturizer, the MOEs between the critical effect levels and the estimates of exposure listed in Table 7-6 are below 10 000, which accounts for uncertainties with respect to interspecies extrapolation, intraspecies extrapolation, the POD, and the adequacy of the database but are considered potentially inadequate.

7.1.4 Uncertainties in evaluation of risk to human health

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

Table 7-7. Source of uncertainty in the risk characterization for bay oil

Key source of uncertainty	Impact
When calculating the risk from methyl eugenol in bay oil for aromatic diffuser, massage oil, body moisturizer, and bath oil product, it was assumed that the source of bay oil contained 2% methyl eugenol. Reported methyl eugenol concentrations in bay oil can vary from 0% to 2%, depending on the source.	+
There are no short-term, chronic, reproductive/developmental toxicity, or carcinogenicity studies identified for bay oil.	+/-
Route-to-route extrapolation for bay oil was carried out for dermal and inhalation scenarios in comparison to an effect level from an oral study.	+/-

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

7.2 Tarragon oil

7.2.1 Exposure assessment

Environmental media

No uses were indicated in CEPA section 71 survey data for tarragon oil. No reports of monitoring for tarragon oil in environmental media in Canada or elsewhere were identified. According to information considered under the ERC, tarragon oil was classified as having a low ecological exposure potential (see section 6.1).

Food

No definitive information is available concerning the potential use of tarragon oil as a food flavouring agent in foods sold in Canada. However, since tarragon oil is known to be used as a food flavouring agent internationally, it is possible that this substance is present as a flavouring agent in foods sold in Canada.

The per capita (“individual”) estimated intake of tarragon oil as a food flavouring agent is $5.37 \times 10^{-1} \mu\text{g}/\text{kg bw}/\text{day}$ (Burdock 2010). This estimate was based on annual production volumes reported by the food industry (NAS 1989 as cited in Burdock 2010) and assumes that only 60% of the actual volume produced was reported and that the entire amount produced was consumed by only 10% of the US population.

In the absence of data on the actual use, if any, of tarragon oil, as a flavouring agent in foods sold in Canada, the per capita intake estimates for the US population (Burdock 2010) are acceptable estimates of possible Canadian dietary exposure for the population 1 year of age and older to this substance from its use as a food flavouring agent.

Trans-anethole in breast milk was detected following ingestion of capsules containing 100 mg of trans-anethole by 15 lactating women (Hausner et al. 2008). Concentration of trans-anethole peaked ~2 to 6 hours post consumption (23.2 $\mu\text{g}/\text{L}$) and returned to baseline within 8 hours post ingestion.

Exposure from natural occurrence in foods

No definitive information is available concerning the natural occurrence of tarragon oil in foods. Tarragon oil is obtained from plant material of the named plant source (Burdock 2010; VCF 2020). There is expected to be little dietary exposure, if any, to this substance from its natural presence in foods (Nijssen et al. 2018).

Products available to consumers

Tarragon oil is present in products available to consumers. To evaluate the potential for exposure to tarragon oil from cosmetics and NHPs applied by the dermal route, sentinel scenarios were selected based on a combination of use frequencies and reported concentrations of tarragon oil in these products. The selected sentinel cosmetic scenarios represented the highest exposures, relative to other dermally applied cosmetics as well as NHPs where tarragon oil is used as an NMI, based on identified products reported to contain this substance. Exposures to tarragon oil from the use of body moisturizer, body fragrance, facial moisturizer, facial cleanser, and soap were considered to be the sentinel scenarios for dermal applications (personal communication, email communication from the Consumer and Hazardous Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced).

For the use of 100% tarragon oil in DIY products, the highest daily exposures are expected to occur from DIY aromatic diffuser with a reported upper concentration of

100%, the use of a body moisturizer diluted to a concentration of 3% (Tisserand institute 2021), a DIY massage oil diluted to a concentration of 3% (RIVM 2006), and a DIY bath oil product with a reported upper concentration of 100%.

Tarragon oil is also present as an NMI for the purpose of flavour enhancement in oral NHPs; oral exposure to tarragon oil was therefore quantified for such products (LNHPD 2021). The non-medicinal role of tarragon oil when used as a flavour enhancer is associated with an oral restriction of up to 0.05 mg/kg bw/day (NHPID [modified 2021]). This restriction is recommended in Tisserand and Young (2014) based on the estragole and methyl eugenol content in tarragon oil and the potential genotoxic and carcinogenic effects of estragole and methyl eugenol. When tarragon oil is used topically, this restriction is up to 0.12% (Tisserand and Young 2014).

In the absence of any chemical-specific dermal absorption data, a dermal absorption value of 40% for methyl eugenol was used to estimate systemic exposure from dermal exposure (EC, HC 2010). To account for the amount of product absorbed by the dermal route, the product amount available for inhalation was adjusted by 60%, except for body moisturizer. For body moisturizer, since the product amount for inhalation was adjusted for the exposed surface area, and since this value was less than 60% of the product amount, no further adjustment was made to the product amount.

The systemic daily exposures were estimated by summing exposures via all relevant routes for the scenario (oral, dermal, inhalation). Exposure estimates for the lowest and highest exposed age groups from products, as well as calculated LADDs, are summarized in Table 7-8.

In addition, systemic daily exposure estimates for the lowest and the highest exposed age groups and LADDs for tarragon oil from DIY products are summarized in Table 7-9.

Table 7-8. Estimated daily and lifetime amortized exposures to tarragon oil from products available to consumers

Product scenario	% in product	Systemic daily exposure (mg/kg bw/day) ^a	LADD ^b (mg/kg bw/day)
Body moisturizer	0.3%	1.59 x 10 ⁻¹ (14–18 years) to 3.07 x 10 ⁻¹ (0–5 months)	1.75 x 10 ⁻¹
Body fragrance	100%	3.12 (14-18 years) to 4.68 (4–8 years)	3.44
Facial moisturizer	0.1%	1.05 x 10 ⁻² (14–18 years) to 1.75 x 10 ⁻² (adults)	1.46 x 10 ⁻²
Facial cleanser	0.1%	2.68 x 10 ⁻⁴ (14–18 years) to 3.70 x 10 ⁻⁴ (9–13 years)	2.73 x 10 ⁻⁴
Soap	0.3%	3.64 x 10 ⁻⁴ (adults) to 4.78 x 10 ⁻⁴ (1 year)	3.86 x 10 ⁻⁴
Digestive aid capsule (NHP)	0.0026%	1.26 x 10 ⁻⁴ (adults)	9.57 x 10 ⁻⁵

¹Only lowest and highest exposed age groups are presented.

²See Appendix A for calculation details.

Table 7-9. Estimated daily and lifetime amortized exposures to tarragon oil from DIY products

Product scenario	% in product	Systemic daily exposure (mg/kg bw/day) ^a	LADD ^b (mg/kg bw/day)
Aromatic diffuser	100%	1.09 (adults) to 1.96 (1 year)	1.20
Massage oil	3%	6.25 x 10 ⁻²² (adults) to 4.56 x 10 ⁻¹ (0–5 months)	8 x 10 ⁻²
Bath oil product	100%	4.30 x 10 ⁻² (adults) to 6.95 x 10 ⁻² (9–13 years)	4.05 x 10 ⁻²
Body moisturizer	3%	1.59 (14–18 years) to 3.07 (0–5 months)	1.75

^aOnly lowest and highest exposed age groups are presented.

^bSee Appendix B for calculation details.

7.2.2 Health effects assessment

There are no empirical health effects data available and no international assessments for tarragon oil, except for an unscheduled DNA synthesis (UDS) assay in rat liver (Nesslany et al. 2010) and an Ames test with *Saccharomyces cerevisiae* (*in vitro* study) (Tateo et al. 1989), which both showed positive results.

In order to inform the health effects assessment, the hazard information available for the main components of tarragon oil, methyl eugenol (2%–39%), estragole (0%–82%), sabinene (trace–39%), terpinolene (0.5%–25%), cis-anethole (51%–81%), trans-anethole (21.1%–53%), and elemicin (trace–57%) were considered.

Methyl eugenol

Methyl eugenol is determined to be a genotoxic carcinogen, and its BMDL₁₀ is 22.2 mg/kg bw/day. Further information on the health effects of methyl eugenol is provided in the Health Effects Assessment section for bay oil (section 7.1.2).

Estragole

Estragole was determined to be a similar genotoxic carcinogen to methyl eugenol by the OEHHA, EFSA, IFRA, and European Medicines Agency (EMA) (OEHHA 1999; EFSA 2009; IFRA 2015; EMA 2020). IFRA calculated a reference dose for fragrances of 0.04 mg/kg bw/day for long-term exposure (IFRA 2015). EFSA determined BMDL₁₀ values of between 9.2 mg/kg bw/day and 32.7 mg/kg bw/day based on the 12-month carcinogenic study from Miller et al. (1983), and the EMA used these same values for its risk assessment of estragole (EMA 2015). However, in the carcinogenic study, animals

were exposed via the diet, and the authors of the study did not provide the amount of treated food consumed by animals. In addition, EFSA did not provide the justification and the calculation of the estimated daily dose of estragole that they used to derive the BMDL₁₀ values.

In carcinogenicity oral studies, male and female preweaning CD-1 mice were administered 2.5 mmol estragole/kg bw (equivalent to 370 mg/kg bw) by gavage twice a week for 5 weeks (Miller et al. 1983). Within 11 to 14 months following the last day of exposure, a significant increase of hepatomas was observed in male mice but not in female mice (Miller et al. 1983).

In another carcinogenicity study by the same authors, adult female CD-1 mice (50/dose) were administered 0, 2300, or 4600 mg/kg diet, 3 times per week for 12 months. A subset of animals had a 6-month recovery period without treatment (Miller et al. 1983). All animals fed with estragole showed a significantly higher number of hepatic angiosarcomas, hemangioendotheliosarcomas, and hepatomas (Miller et al. 1983). In addition, nodules in the liver were observed in both estragole groups at 12 months, but nodules gradually regressed after administration because they were reduced at 18 months (Miller et al. 1983). Livers showed various degrees of chronic inflammation, fibrosis, bile duct proliferation, and number of ceroid-laden histocytes and cellular hyperplasia and megalocytosis (Miller et al. 1983). The authors of the study did not provide a measure of the consumption of estragole by animals during the treatment, which impeded the ability to estimate daily exposure.

In a carcinogenicity study, preweaning male CD-1 mice (50/dose) were exposed to 0, 4.4 or 5.2 $\mu\text{mol/kg bw}$ (equivalent to 0, 651, or 769.6 $\mu\text{g/kg bw}$, respectively) in total after 4 subcutaneous injections on postnatal days (PNDs) 1, 8, 15, and 22 (Drinkwater et al. 1976). At 15 months, the number of hepatocellular carcinomas in treated animals was higher than in control animals (Drinkwater et al. 1976).

Overall, the animal laboratory studies showed a clear carcinogenic potential of estragole.

In a 90-day study, male and female F344/N rats were orally administered 0, 37.5, 75, 150, 300, or 600 mg/kg bw/day estragole by gavage for 5 days per week (NTP 2011a). No mortality was observed, but a significant decrease in mean body weight or body-weight gain was observed at 300 and 600 mg/kg bw/day in both sexes of rats. Hematological parameters showed statistically significant and dose-dependent changes in male or female rats, which included microcytic, normochromic, and nonresponsive anemia. Changes in hematological parameters were reported to intensify with duration and dose, ranging from subtle alterations at low dose exposure to statistically significant changes observed in the 300 or 600 mg/kg bw/day dose groups at study termination (week 14 of exposure). The study authors suggested that the hematological changes are indicators of ineffective erythropoiesis (NTP 2011a). The authors also reported bone marrow hyperplasia, increase in kidney weight, changes in tubular histology, degeneration of olfactory epithelium, hypertrophy of chromophobe cells in the pars

distalis of the pituitary gland, atrophy of gastric glands and testes, and increase in the incidence of degeneration of germinal epithelium of testis and bilateral hypospermia at 300 and 600 mg/kg bw/day in both sexes (NTP 2011a). The level of enzymes including serum alanine aminotransferase, sorbitol dehydrogenase, and bile salt increased significantly, and these changes were consistent with histopathological lesions observed at 300 and 600 mg/kg bw/day in the liver of both sexes. Gross changes showed a significant increase in absolute and relative liver weight and discoloration followed by a histopathological evaluation of liver, which exhibited a dose-dependent increase in hepatocyte hypertrophy, oval cell hyperplasia, bile duct hyperplasia, and evidence of chronic inflammation in all dose groups in both sexes (NTP 2011a). Hepatocellular adenoma was observed in 1/10 male rats, and cholangiocarcinoma (bile duct cancer) was present in 2/10 male rats at 600 mg/kg bw/day. The study authors concluded that the liver was the primary target organ of estragole in rats (NTP 2011a).

In a 90-day study, male and female B6C3F1 mice were orally administered 0, 37.5, 75, 150, 300, or 600 mg/kg bw/day estragole by gavage for 5 days per week (NTP 2011a). Estragole treatment caused death in one male mouse at 600 mg/kg bw/day during week 9. All female mice died during week 1 after exposure to 600 mg/kg bw/day, which the study authors linked to liver necrosis caused by estragole (NTP 2011a). As was observed in rats, the study authors reported liver as the target organ in mice based on increased liver weight, hepatocyte hypertrophy, hepatocellular degeneration, oval cell hyperplasia, and necrosis in all dose groups except for 37.5 mg/kg bw/day (NTP 2011a). Statistically significant degeneration of the gastric glands of the glandular stomach, squamous hyperplasia, mineralization, and forestomach ulcer and degeneration of olfactory epithelium were observed mostly at 300 and 600 mg/kg bw/day (NTP 2011a).

Overall, the study authors concluded that liver was the primary target organ in male and female rats and mice following subchronic 90-day exposures to estragole. Estragole was also reported to show carcinogenic activity. However, it was acknowledged that this 90-day exposure study did not assess the full carcinogenic potential of estragole (NTP 2011a). It was also acknowledged in the NTP study (2011a) that ample studies have shown hepatocarcinogenic potential of estragole or structurally related substances (safrole or methyl eugenol) in rats and mice following long-term exposure.

However, the available literature cannot be used to derive a BMDL₁₀. In the absence of adequate dose-response studies on estragole, a read-across approach was taken, and hazard information on the read-across analogue, methyl eugenol, was used to characterize the carcinogenic risk.

Results of genotoxicity testing of estragole were generally negative in *Salmonella typhimurium* (*S. typhimurium*) (Drinkwater et al. 1976; Swanson et al. 1979; Sekizawa and Shibamoto 1982; NTP 2011a) and in the *Bacillus subtilis* Rec assay (Sekizawa and Shibamoto 1982), but also in hamster V79 cells likely due to the complex metabolism required for bioactivation *in vivo*. Positive results were reported for estragole when the

putative toxic metabolites, namely 1'-hydroxyestragole and allyl epoxides, were positive in mutagenicity assays with or without exogenous activation (EMA 2020).

Estragole was positive in V79 cells with the sister chromatid exchange assay and the alkaline comet assay and in two CHO cell lines with the Comet assay (Martins et al. 2012). All assays were positive without metabolic activation, suggesting that estragole, besides being metabolized to genotoxic metabolites, may also be a direct-acting genotoxic that forms DNA adducts. Several *in vivo* studies in adult rodents showed that the genotoxicity of estragole itself is induced by DNA adducts detected with UDS assay in liver (Phillips et al. 1984; Randerath et al. 1984; Nessler et al. 2010; Paini et al. 2012; Suzuki et al. 2012), in lungs and kidneys (Paini et al. 2012), and *in vitro* in human hepatoma (HepG2) cells (Zhou et al. 2007). Estragole is considered to be genotoxic by specifically producing DNA adducts in animal models and human liver cells and is considered carcinogenic in animal models.

Estragole is an alkenylbenzene and is structurally related to methyl eugenol (IARC 2014). Chemically, estragole is 4-methoxyallylbenzene, and methyl eugenol is 3,4-dimethoxyallylbenzene. The only structural difference between estragole and methyl eugenol is that the latter contains a second ring methoxy group. Since they contain the same skeletal structure and ring substituents, both substances are expected to exhibit similar metabolic fate, pharmacokinetics, and toxicological potential. All have comparable physicochemical properties and mechanistic profiles, are bioavailable, and test positive for carcinogenicity (genotox) in OECD QSAR Toolbox (OECD QSAR Toolbox 2016). Methyl eugenol and estragole are metabolized primarily by CYP1A2 that produce similar genotoxic and carcinogenic metabolites (IARC 2014). Methyl eugenol, as estragole, is not mutagenic in bacteria but induces chromosomal aberrations *in vitro* and DNA adducts in the liver of rodents *in vivo* and in human liver cells *in vitro* (IARC 2014).

Sabinene

The only health effects information available for sabinene is a positive result in a bacterial reverse mutation assay using *S. typhimurium* strain TA 1535 in the absence or presence of metabolic activation (ECHA Registration dossier 2017). In the absence of genotoxicity, carcinogenicity, or reproductive/developmental toxicity data of sabinene, the EFSA used a NOAEL of 222 mg/kg bw/day for beta-caryophyllene (bicyclic, non-aromatic hydrocarbon group) as a supporting substance for its assessment of sabinene (EFSA 2015).

Terpinolene

Carcinogenicity studies were not identified for terpinolene.

Terpinolene was neither irritating nor a sensitizer to human skin at a concentration of 20% in petrolatum applied for 48 hours under a patch (Opdyke 1988).

In a reproductive and developmental toxicity study conducted according to OECD test guidelines, 422 male and female Sprague-Dawley rats (10/dose/sex) were orally administered 0, 800, 2500, or 5000 ppm (equivalent to 0, 54.1, 154.6, or 300.8 mg/kg bw/day, respectively) terpinolene by diet during pre-mating and mating periods for both sexes (up to 42 days for males) and during gestation and early lactation for females only (approximately 100 days for females) (ECHA Registration dossier 2020a). Some males had a recovery period of 2 weeks. No mortality or clinical signs were observed by study authors. A significant reduction in body weight and dietary intake was observed in males and females in the 5000 ppm group and in females in the 2500 ppm group. A reduction in body weight was also observed in females in the 800 ppm group. Study authors concluded that body weight effects were a result of the low palatability of the diet (ECHA Registration dossier 2020a). No treatment-related effects were detected in mating performance, fertility, or gestation lengths by study authors. Only males in the 5000 ppm group showed an increase in liver weight (absolute and relative to body weight). Males in the 2500 and 5000 ppm groups showed centrilobular hepatocellular hypertrophy, which was reversible following 2 weeks without treatment. Reduced pup body weight at PND 7 was detected in the 5000 ppm litter group. On the basis of these results, study authors determined NOAELs for general toxicity of 151.5 and 294.6 mg/kg bw/day (2500 and 5000 ppm) for females and males, respectively, a NOAEL for maternal and developmental toxicity of 2500 ppm (corresponding to 356 mg/kg bw/day), and a NOAEL for reproductive toxicology of 5000 ppm, the highest dose tested (corresponding to 294.6 mg/kg bw/day) (ECHA Registration dossier 2020a).

Terpinolene was not genotoxic in the micronucleus assay or sister chromatid exchanges assay and had no effect on 8-oxo-2-deoxyguanosine level in cultured human blood cells (Turkez et al. 2014). Terpinolene was also not genotoxic in the gene mutation test, Ames test, chromosome aberration test, and micronucleus assay in human lymphocytes with or without metabolic activation (ECHA Registration dossier 2020a).

Cis-anethole and trans-anethole

Both anetholes are distributed and metabolized similarly in rats, rabbits, humans, and mice (Tisserand and Young 2014). Trans-anethole undergoes biotransformation by three principal pathways: O-demethylation, N-oxidation, and epoxidation. The third pathway can lead to toxic metabolites and is considered a minor pathway (3%) in humans (Tisserand and Young 2014). In rodents, trans-anethole is metabolized differently depending on dose, but this is not the case in humans (Tisserand and Young 2014).

Cis-anethole is also called (Z)-anethole and is significantly more toxic than the common (E)-anethole (trans-anethole) (Tisserand and Young 2014). Both cis- and trans-anethole are considered to be isomers of estragole (US NLM 2014). The LD₅₀ for the oral route was determined to be 150 mg/kg for cis-anethole in rats (RTECS 2019). There are no other empirical health effects data available for cis-anethole.

In Australia, trans-Anethole was previously reviewed by NICNAS in a 2016 priority existing chemical assessment, and the only health effect reported was skin sensitization (NICNAS 2016a). A safety evaluation of trans-anethole by the WHO concluded that trans-anethole is unlikely to be genotoxic, but insufficient data were available to permit a final evaluation of the significance of the malignant liver tumours observed in rodents (WHO 1991). A NOAEL of 300 mg/kg bw/day was determined by the WHO on the basis of hepatocellular hypertrophy in rats at 600 mg/kg bw/day after a 90-day oral exposure (WHO 1999).

Male and female CD-1 mice (5/sex/dose) were orally administered 0, 60, 120, 240, 360, or 500 mg/kg bw/day trans-anethole by diet for 28 days (Newberne et al. 1999). Study authors observed that the addition of trans-anethole to the diet resulted in a very low palatability for mice in higher doses, resulting in decreased food intake and body weight gain (Newberne et al. 1999). No clinical or histopathological changes were observed (Newberne et al. 1999).

The same authors then used the previous study to establish the dose range for a 90-day study. Male and female CD-1 mice (20/sex/dose) were orally administered 0, 30, 60, 120, or 240 mg/kg bw/day trans-anethole by diet for 90 days (Newberne et al. 1999). Increased mortality was observed at doses of 60 mg/kg bw/day and higher in males and at 120 mg/kg bw/day and higher in females. Study authors attributed these deaths to “inanition syndrome” characterized by decreases in food consumption, water intake, and physical activity, presumably associated with palatability of the diet (Newberne et al. 1999). Body weight decreased weekly at doses of 120 mg/kg bw/day and greater in males and at 240 mg/kg bw/day for females, accompanied by a decrease in daily food consumption. Gross and histopathological evaluation showed a reduction in liver glycogen at doses of 30 mg/kg bw/day and greater in males and at 60 mg/kg bw/day and greater in females. Reduced kidney, brain, and spleen weight in males at the highest dose was observed and correlated with decreased cellularity in these organs (Newberne et al. 1999). An increase in hepatocellular hypertrophy in males at doses of 60 mg/kg bw/day and greater as well as enlarged livers and a dose-dependent increase in relative liver weights in all groups of treated males was observed. Study authors considered these effects to be adaptive physiological responses resulting from the known metabolic pathways of trans-anethole in rodents (Newberne et al. 1999). No other difference, especially in histopathology, was observed between any group of treated females and controls. Blood chemical analysis revealed an increase in alanine and aspartate transaminase values at doses of 120 mg/kg bw/day and greater, which, in conjunction with hepatocyte hypertrophy, suggests enzyme induction according to the study authors’ conclusion (Newberne et al. 1999). An increase in alkaline phosphatase at doses of 120 mg/kg bw/day and greater was also observed in all treated animals. With the exception of the reduction in hepatocellular glycogen, no adverse effects were observed in the liver of female mice (Newberne et al. 1999). On the basis of the lack of any evidence of histopathology, a minimal change in blood serum, and the large decrease in dietary intake as a result of the unpalatability of the food in both sexes, the study authors assigned a NOAEL of greater than 240 mg/kg bw/day (Newberne et al. 1999). Since there was no recovery time to confirm that the effects seen in the liver,

kidney, brain, and spleen of males were adaptive, a LOAEL of 30 mg/kg bw/day was determined on the basis of the dose-dependent liver toxicity in male mice.

In a reproductive study, male and female Wistar rats were administered 0% or 1% trans-anethole (actual dose of trans-anethole varied from 1400 mg/kg bw/day in the earlier weeks of treatment to 700 mg/kg bw/day at the end of the pre-mating period) in diet for 70 days (WHO 1999; ECHA Registration dossier 2020b). The rats were mated on a one-to-one basis for a maximum of 15 days, with 9 pairs of rats fed control diet (group I), 9 pairs fed treated diet (group IV), 10 pairs of males fed control diet and 10 pairs of females fed treated diet (group II), and 10 pairs of males fed treated diet and 10 pairs of females fed control diet (group III). After weaning, the offspring received the same dietary treatment as both of their parents. Feeding of the appropriate diet was maintained during pre-mating, mating, gestation, and lactation. Four generations were thus produced by following the same pattern. In addition, a cross-fostering experiment was conducted by mating six control and six treated females from the F1 generation with an equal number of F1 control males. At birth, the litters of control and treated dams were exchanged, and the litters were reared by a dam from the other group (WHO 1999; ECHA Registration dossier 2020b). All groups of rats treated with trans-anethole showed reduced body weight gain. Food consumption was reduced in the treated rats during the initial weeks of the study but was mostly comparable to that of the control group for the remainder of the treatment period, except in F2 males and females, the food consumption of which was significantly lower than that of the controls throughout the pre-mating period. There was no difference in reproductive parameters such as fertility index, gestation index, and pup viability or litter size (WHO 1999; ECHA Registration dossier 2020b). No clinical signs were observed by the study authors. The pup body weights per litter were reduced for all pups reared by treated dams, regardless of the diet fed to the males or to the dams during gestation. Thus, post-natal growth was influenced by the exposure of the dams to trans-anethole during lactation but not gestation; it was suggested by the study authors that the test material may be directly toxic via the milk rather than by an effect on the quality of nutrition (WHO 1999; ECHA Registration dossier 2020b).

In a one-generation reproductive study, female Sprague-Dawley rats (10/dose) were administered 0, 35, 175, or 350 mg/kg bw/day trans-anethole by gavage for 7 days before mating, 7 days during mating with untreated males, 21 days of gestation and then parturition, and up to day 4 of lactation (around 40 days in total) (WHO 1999). The body weights and food consumption of females in the high-dose group were significantly lower during the pre-mating, gestation, and lactation periods (WHO 1999). The same trend was observed in the middle-dose group but was not significant. During lactation, some of the animals in the high-dose group appeared to be in poor condition, as indicated by clinical observations such as emaciation, pale ungroomed coat, and stained fur (WHO 1999). Mating performance and fertility were not modified by treatment; however, an increase in stillborn pups, a decrease in liveborn pups (viability index), and a decrease in pup weight in the high-dose group were observed (WHO 1999). No such effect was seen in the low- and middle-dose groups. A NOAEL was established at 175 mg/kg bw/day (WHO 1999).

In a carcinogenicity study, male and female Sprague-Dawley rats (26-78/dose) were orally administered 0, 0.25, 0.5, or 1% trans-anethole (equivalent to 0, 100, 200, or 400 mg/kg bw/day for females and 0, 120, 250, or 550 mg/kg bw/day for males, respectively) by diet for 2 years (Truhaut et al. 1989). No clinical signs or mortality related to the treatment were observed. A transient retardation of body weight gain as a result of reduced food intake during the first weeks of treatment was noticed in both sexes (Truhaut et al. 1989). No toxicological effects were observed. Some neoplastic lesions were seen in the high-dose female group, such as hepatocellular adenomas and hepatocellular carcinomas, and non-neoplastic lesions in both sexes were observed in the high-dose group, while nodular hyperplasia was observed in males in the medium-dose group (Truhaut et al. 1989). The finding of this study was reviewed by independent pathologists, all of whom agreed that there was a clear increase in hepatocellular adenoma and/or carcinoma in females in the high-dose group (1%) but not in males at any dose level (WHO 1991).

Multiple studies *in vitro* showed that trans-anethole was not genotoxic in Ames assay using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 (Hsia et al. 1979; Swanson et al. 1979; Nestmann et al. 1980; Sekizawa and Shibamoto 1982; Mortelmans et al. 1986; Heck et al. 1989; Gorelick 1995), in chromosomal aberration assay (Gorelick 1995), and in UDS assay (Heck et al. 1989; Marshall et al. 1989; Howes et al. 1990; Müller et al. 1994). Trans-anethole was also not genotoxic in either the *in vivo* micronucleus test in male Swiss mice (Abraham 2001) or the *in vivo* UDS assay (Marshall and Caldwell 1996). Trans-anethole was positive only in the mouse lymphoma assay in the presence of metabolic activation (Heck et al. 1989; Gorelick 1995).

Elemicin

Elemicin is an alkenylbenzene that is structurally related to methyl eugenol. It differs in that it has an additional methoxy group on the fifth carbon of the phenyl ring. A search of toxicological databases revealed a lack of hazard data for elemicin, with no chronic, short-term, developmental, or other animal studies identified.

In an *in vitro* UDS assay, metabolism of elemicin via the 1'-hydroxylation pathway resulted in DNA adduct formation via the same mechanism as methyl eugenol (Hasheminejad and Caldwell 1994). Additionally, elemicin has been shown to cause DNA breaks in a UDS assay in turkey fetal liver (Kobets et al. 2016) and in an *in vitro* cultured rat hepatocyte study (Hasheminejad and Caldwell 1994). There is no other hazard information on elemicin.

A comparison of elemicin with methyl eugenol shows that both have comparable physicochemical properties and mechanistic profiles, are bioavailable, and have alerts for OECD DNA binding, for *in vivo* mutagenicity, and for carcinogenicity (genotox) in OECD QSAR Toolbox (OECD QSAR Toolbox 2016). Methyl eugenol was the most similar analogue proposed (78.57%) by OECD QSAR Toolbox. Given these similarities, methyl eugenol is assumed in this assessment to be a suitable analogue for elemicin.

7.2.3 Characterization of risk to human health

Methyl eugenol, estragole, and elemicin were determined to be the main components of toxicological significance for tarragon oil. All three components are considered to be genotoxic and carcinogenic, with similar modes of action and potency. A BMDL₁₀ of 22.2 mg/kg bw/day for methyl eugenol (Suparmi et al. 2019) was selected to characterize the risk resulting from the methyl eugenol, estragole, and elemicin in tarragon oil.

Taking into consideration the reported concentrations of methyl eugenol (2%–39%), estragole (0%–82%), and elemicin (0%–57%) in tarragon oil, it was assumed that the sum of methyl eugenol, estragole, and elemicin in tarragon oil was 100%.

The LADDs and resulting MOEs for tarragon oil when used as a food flavouring agent and in products available to consumers are summarized in Table 7-10. In addition, LADDs and resulting MOEs from DIY products were calculated and are summarized in table 7-11.

Table 7-10. LADDs and resulting MOEs for tarragon oil in food and products available to consumers

Exposure scenario	LADD ^a (mg/kg bw/day)	MOE ^b
Food flavouring agent (1 year of age and older)	5.37×10^{-4}	>41 000
Systemic exposure by the dermal and inhalation routes from body moisturizer (0.3%)	1.75×10^{-1}	127
Systemic exposure by the dermal and inhalation routes from body fragrance (100%)	3.44	6
Systemic exposure by the dermal and inhalation routes from a facial moisturizer (0.1%)	1.46×10^{-2}	1563
Systemic exposure by the dermal and inhalation routes from a facial cleanser (0.1%)	2.73×10^{-4}	>80 000
Systemic exposure by the dermal and inhalation routes from a soap (0.3%)	3.85×10^{-4}	>57 000
Systemic exposure by the oral route from a digestive aid capsule (NHP) (0.0026%)	9.57×10^{-5}	>200 000

^a Calculation details are summarized in Appendix A.

^b The MOEs were calculated using a BMDL₁₀ of 22.2 mg/kg bw/day based on the carcinogenicity of methyl eugenol.

Table 7-11. LADDs and resulting MOEs for tarragon oil in DIY products

Exposure scenario	LADD ^a (mg/kg bw/day)	MOE ^b
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Systemic exposure by the dermal and inhalation routes from DIY aromatic diffuser (100%)	1.20	18
Systemic exposure by the dermal and inhalation routes from DIY massage oil (3%)	8×10^{-2}	278
Systemic exposure by the dermal and inhalation routes from DIY bath oil product (100%)	4.05×10^{-2}	549
Systemic exposure by the dermal and inhalation routes from DIY body moisturizer (3%)	1.75	13

^a Calculation details are summarized in Appendix B.

^b The MOEs were calculated using a BMDL₁₀ of 22.2 mg/kg bw/day based on the carcinogenicity of methyl eugenol.

MOEs to tarragon oil from food (based on tarragon oil's potential use as a flavouring agent), a digestive aid capsule (NHP), and as a facial cleanser and soap are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk.

However, the MOEs between the critical effect levels and the estimates of daily exposure from body moisturizer, body fragrance, or facial moisturizer are below 10 000. This accounts for uncertainties with respect to interspecies extrapolation, intraspecies extrapolation, the POD, and the adequacy of the database and is considered potentially inadequate. In addition, for exposures to tarragon oil from its use in DIY aromatic diffuser, as DIY massage oil, as a DIY bath oil product, or as a DIY body moisturizer, the MOEs between the critical effect levels and the estimates of exposure listed in Table 7-11 are below 10 000, which accounts for uncertainties with respect to interspecies extrapolation, intraspecies extrapolation, the POD, and the adequacy of the database and is considered potentially inadequate.

7.2.4 Uncertainties in evaluation of risk to human health

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

Table 7-12. Sources of uncertainty in the risk characterization for tarragon oil

Key source of uncertainty	Impact
Tarragon oil was considered to be comprised solely of estragole, elemicin, and methyl eugenol.	+
There are no short-term, chronic, reproductive/developmental toxicity, or carcinogenicity studies identified for tarragon oil.	+/-
A BMDL ₁₀ for methyl eugenol was selected to represent the cancer potency of methyl eugenol, estragole, and elemicin combined.	+/-
There were no suitable studies for the dermal or inhalation route of exposure; therefore, route-to-route extrapolation for tarragon oil was	+/-

carried out for dermal and inhalation scenarios by comparing to an effect level from an oral study.	
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+ = uncertainty with potential to cause overestimation of exposure/risk; - = uncertainty with potential to cause underestimation of exposure/risk; +/- = unknown potential to cause over- or underestimation of risk.

7.3 Phenylpropanoids subgroup 1 (jasmine oil, perfumes and essences of jasmin)

7.3.1 Exposure assessment

Environmental media

In consideration of the low quantity (<100 kg) of the substance submitted in response to a CEPA section 71 survey (Environment Canada 2013), exposure to this substance from environmental media is not expected. No reports of monitoring for jasmine oil in environmental media in Canada or elsewhere were identified.

Food

No definitive information is available concerning the potential use of jasmine oil as a flavouring agent in foods sold in Canada. However, since jasmine oil is identified to be used as a food flavouring agent internationally, it is possible that this substance is present as a flavouring agent in foods sold in Canada.

The Fenaroli's Handbook of Flavour Ingredients reports the per capita ("individual") estimated intake of jasmine oil from its use as a food flavouring agent to be 9.88×10^{-3} µg/kg bw/day on the basis of a MSDI approach for the US population (Burdock 2010).

In the absence of data on the actual use, if any, of jasmine oil as a flavouring agent in foods sold in Canada, the per capita intake estimate for the US population (Burdock 2010) is an acceptable estimate of possible Canadian dietary exposure for the general population 1 year of age and older to this substance from its potential use as a food flavouring agent (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced).

Exposure from natural occurrence in foods

No definitive information is available concerning the natural occurrence of jasmine oil in foods. Therefore, low dietary exposure to this substance, if any, is expected from its natural presence in foods (Nijssen et al. 2018).

Products available to consumers

Jasmine oil is present in products available to consumers. To evaluate the potential for exposure to jasmine oil from cosmetics and NHPs applied by the dermal and inhalation routes, sentinel scenarios were selected based on a combination of use frequencies and reported concentrations of jasmine oil in these products. The selected sentinel scenarios represented the highest exposures, relative to other cosmetics as well as NHPs where jasmine oil is used as an NMI, based on identified products reported to contain these substances. Exposure to jasmine oil from the use of hair conditioner, body cleanser, body moisturizer, facial moisturizer/acne treatment (NHP), topical treatment cream (NHP), body fragrance, aerosol hair styling product, antiperspirant/deodorant, temporary hair colour, sunscreen (NHP), and antiseptic skin cleanser (NHP) were considered to be the sentinel scenarios for dermal applications (personal communication, email communication from the Consumer and Hazardous Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced; personal communication, email communication from the Natural and Non-prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020 and 2021; unreferenced).

Jasmine oil is also present in a lipstick product. Exposure by the oral route from the use of a lipstick was quantified (personal communication, email from the Consumer and Hazardous Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced).

For the use of 100% jasmine oil in DIY products, the highest daily exposures are expected to occur from the use of the oil in aromatic diffuser, massage oil, bath oil product, body moisturizer, and as a facial steamer, with a reported upper concentration of 100%. Although the upper concentration reported for massage oil containing jasmine oil was 100%, massage oils are typically diluted prior to use. Thus, the maximum concentration of jasmine oil in DIY massage oil was assumed in RIVM (2006) to be 3%. It is reported that body products are typically diluted to concentrations of 1% to 4% (Tisserand Institute 2021). On the basis of this information, the maximum concentration of jasmine oil in DIY body moisturizer was assumed to be 3%.

Information from the American Cleaning Institute's website indicates potential use of jasmine oil as a fragrance ingredient in all-purpose cleaners, dish detergent, laundry conditioner, and liquid laundry detergent (ACI 2020). To assess potential exposure to jasmine oil from its use in household cleaning products, exposures from the use of jasmine oil in a liquid and aerosol all-purpose cleaner at a maximum concentration of 1%, a 5% aerosol laundry conditioner, and a 5% liquid laundry detergent for machine-washing were quantified (ACI 2020).

To calculate systemic exposure from dermal exposure to jasmine oil, a dermal absorption value of 50% was selected based on the following considerations. The dermal absorption of benzyl benzoate and benzyl acetate, which are two of the main components of jasmine oil, was determined in an *in vivo* study in rhesus monkeys. Values were obtained in non-occluded and occluded monkey skin. The values of the

dermal absorption in unoccluded site were 34.6% and 57% for benzyl acetate and benzyl benzoate, respectively, with absorption occurring primarily during the first 24 hours after topical administration. The absorption of benzyl benzoate and benzyl acetate may be predictive of the ability of these compounds to be absorbed when applied on human skin (Bronaugh et al.1990).

To estimate systemic exposure for jasmine oil, the estimated oral, inhalation, and dermal exposures were summed, where appropriate. To account for the amount of product absorbed by the dermal route, the product amount available for inhalation was adjusted by 50%, except for body moisturizer. For body moisturizer, since the product amount for inhalation was adjusted for the exposed surface area, and this value was less than 50% of the product amount, no further adjustment was made to the product amount.

Exposure estimates for the lowest and highest exposed age groups from products available to consumers are summarized in Table 7-13. Systemic (sum of inhalation and dermal) daily exposure estimates from DIY products containing jasmine oil are summarized in Table 7-14.

Table 7-13. Estimated daily exposure to jasmine oil from products available to consumers

Product scenario	% in product	Route(s) of exposure	Exposure range (mg/kg bw/day)^a
Hair conditioner (wash-off)	30%	Dermal and inhalation	5.68 x 10 ⁻² (adults) to 6.44 x 10 ⁻² (9–13 years)
Body cleanser (liquid)	3%	Dermal and inhalation	3.71 x 10 ⁻² (adults) to 0.13 (0–5 months)
Body moisturizer	3%	Dermal and inhalation	2.07 (adults) to 4.78 (0–5 months)
Facial moisturizer/acne treatment (NHP)	1%	Dermal and inhalation	0.32 (adults) to 0.40 (9–13 years)
Topical treatment cream (NHP)	1%	Dermal and inhalation	0.11 (adults) to 0.14 (9–13 years)
Facial sun protection powder (NHP)	0.07%	Dermal and inhalation	2.2 x 10 ⁻³ (adults)
De-stress roll-on (NHP)	0.01%	Dermal and inhalation	3 x 10 ⁻⁴ (adults)
Lipstick	3%	Oral	1.78 x 10 ⁻² (adults) to 4.40 x 10 ⁻² (2–3 years)
Body fragrance	82%	Dermal and inhalation	3.12 (14-18 years) to 9.14 (2–3 years)
Aerosol hair styling product	0.1%	Dermal and inhalation	1.58 x 10 ⁻³ (14–18 years) to 4.26 x 10 ⁻³ (4–8 years)

Antiperspirant/deodorant	2%	Dermal and inhalation	0.11 (9–13 years) to 0.18 (14–18 years)
Temporary hair colour	0.1%	Dermal and inhalation	2.42×10^{-2} (adults) to 7.73×10^{-2} (4–8 years)
Sunscreen (NHP)	0.07%	Dermal	7.35×10^{-2} (9–13 years) to 3.32×10^{-1} (6–11 months)
Antiseptic skin cleanser (NHP)	2%	Dermal and inhalation	0.38 (14–18 years) to 1.1 (2–3 years)
Antiseptic skin cleanser (NHP) ^b	2%	Dermal and inhalation	5.67 (adults) to 27.2 (2–3 years)
Aerosol all-purpose cleaner (application and wiping)	1%	Dermal and inhalation	7×10^{-2} (adults)
All-purpose liquid floor cleaner (mixing and loading, and application)	1%	Dermal and inhalation	2.53×10^{-2} (adults)
Post-application exposure to cleaned floors	1%	Dermal, inhalation, and incidental oral (hand-to-mouth)	1.16×10^{-2} (1 year)
Aerosol laundry conditioner	5%	Inhalation	2.45×10^{-2} (adults)
Liquid laundry detergent (machine wash) (mixing and loading, hanging laundry, and wearing recently washed clothing)	5%	Dermal and inhalation	1.86×10^{-1} (adults)
Liquid laundry detergent (machine wash) (migration from washed textiles) (all subpopulations except adults)	5%	Dermal, inhalation, and incidental oral (object-to-mouth) (1 year only)	5.54×10^{-3} (14–18 years) to 9.28×10^{-3} (0–6 months)

^a Only the lowest and highest exposed age groups are presented. See Appendix A for calculation details.

^b For situations of public health concern, the use of hand sanitizers among the general population may increase up to 25 uses per day (personal use by adults, increased use by children in schools and childcare facilities) (RIVM 2021a).

Table 7-14. Estimated daily exposure to jasmine oil from DIY products

Product scenario	% in product	Route(s) of exposure	Exposure range (mg/kg bw/day) ^a
Aromatic diffuser	100%	Inhalation and dermal	1.16 (adults) to 1.97 (9–13 years)

Massage oil	3%	Dermal and inhalation	6.89 x 10 ⁻¹ (adults) to 4.35 (0–5 months)
Bath oil product	100%	Dermal and inhalation	1.56 x 10 ⁻¹ (adults) to 2.51 x 10 ⁻¹ (9–13 years)
Body moisturizer	3%	Dermal and inhalation	2.07 (adults) to 4.78 (0–5 months)
Facial steamer	100%	Dermal and inhalation	1.05 to 1.19 ^b (adults) 3.13 to 3.47 ^b (4–8 years)
Facial steamer - bystander exposure (1 year only)	100%	Dermal and inhalation	5.26 x 10 ⁻¹

^a Only the lowest and highest exposed age groups are presented. See Appendix A for calculation details.

^b After a total of 4 hours of exposure; once the device is turned off after 20 minutes of use, it is assumed that the person remains in the room for 3 hours and 40 minutes.

7.3.2 Health effects assessment

There are limited empirical health effects data available and no international assessments for jasmine oil.

In a reproductive study, female rats (10/dose) were administered 0 or 500 mg/kg bw/day *Jasmine officinale* var. *grandiflorum* by gavage from 3 estrus cycles (approximately 15 days), which induced a significantly longer dioestrus cycle in treated rats (Iqbal et al. 1993). Study authors did not give any details on clinical signs or effects from the treatment.

In another reproductive study from the same authors, female rats were administered 0, 250, or 500 mg/kg bw/day *Jasmine officinale* var. *grandiflorum* extract (jasmine extract) in drinking water from gestation days (GDs) 1 to 5 (15 rats/dose), or from GDs 8 to 12 (8 rats/dose), or from GDs 12 to 20 (6 rats/dose) (Iqbal et al. 1993). Animals treated from GDs 1 to 5 were euthanized at GD 10, while the other animals were euthanized at GD 20. Study authors did not give any details about the clinical state of treated animals. A dose-dependent increase in implantation loss (control: 1.42%, low dose: 48.8%, high dose: 75%) and a dose-dependent decrease in fertility (control: 100%, low dose: 92%, high dose: 60%) was observed from GDs 1 to 5. A higher fetus mortality was observed at the highest dose (12.8%) in comparison with control (1.2%). A dose-dependent increase in resorption (control: 3.44%, low dose: 7.89%, high dose: 15.35%), was observed from GDs 8 to 12. There were no significant changes in fetal weight and length, and no gross abnormalities were observed from GDs 12 to 20. However, authors of the study did not analyze the skeleton or any organs of the fetuses. A decrease in progesterone was observed at GD 5 but not at GDs 12 and 20 in all treated animals,

which indicates that jasmine oil may have an endocrine-disrupting effect during early pregnancy. Study authors concluded that the decrease in progesterone levels on GD 5 may be responsible for the anti-implantation in female rats (Iqbal et al. 1993). Based on the study's results, a LOAEL of 250 mg/kg bw/day, the lowest dose tested, was determined for female reproductive and developmental toxicity.

In order to inform the health effects assessment, the hazard information available for the main components of jasmine oil, benzyl acetate (0%–31%), benzyl benzoate (3%–21%), (E,E)-alpha-farnesene (1%–6%), linalool (7%–13%), phytol (11%–26%), isophytol (5%–12%), and nerolidol (trace–13%), have been considered.

Benzyl acetate and benzyl benzoate

There are no empirical health effects data available for benzyl acetate, and only two reproductive and developmental studies are available for benzyl benzoate.

Benzyl acetate and benzyl benzoate were included by the US EPA as benzyl esters under the chemical category “benzyl derivatives” (US EPA 2010). Benzyl acetate and benzyl benzoate are hydrolyzed to yield benzyl alcohol, which is subsequently oxidized to benzoic acid as a stable metabolite (US EPA 2010). Because they contain a benzene ring bonded directly to an oxygenated functional group that is hydrolyzed and/or oxidized to benzoic acid, these substances and other benzyl derivatives were placed in the same category (US EPA 2010). After a complete review of the toxicokinetics of benzyl acetate and benzyl benzoate, other international agencies such as EFSA, the Research Institute for Fragrance Materials (RIFM), or the Cosmetic Ingredient Review (CIR) supported the rapid and strong metabolism of both substances into benzoic acid (EFSA 2012; McGinty et al. 2012; Johnson et al. 2017).

In 2019, ECCC and HC assessed several substances belonging to the Benzoates Group, and all were esters of benzoic acid (ECCC, HC 2019). The characterization of the hazard of all three subgroups in the Benzoates Group screening assessment (that is, simple alkyl benzoates, dibenzoates, and tribenzoates) was strongly linked with empirical evidence that these substances will readily hydrolyze into benzoic acid, which is then further metabolized into hippuric acid and subsequently excreted (ECCC, HC 2019). As a consequence, and in concordance with other jurisdiction assessments, the screening assessment on the Benzoates Group concluded that these substances exhibit low hazard properties and the potential risk to human health is considered to be low (ECCC, HC 2019).

However, benzyl benzoate seems to potentially induce adverse developmental effects. Pregnant Wistar rats (5/dose) were administered 0, 25, or 100 mg/kg bw/day benzyl benzoate by gavage from GDs 0 to 20 (Koçkaya and Kılıç 2011). A decrease in food and water consumption was measured in the animals of the high-dose group, but no changes in body weight or body weight gain were observed. A significant higher percentage of lymphocytes and a lower percentage of monocytes were observed in the high-dose group as well as a decrease in creatinine levels. An increase in aspartate

aminotransferase was measured in both treated groups. Absolute heart weight in dams was higher in the high-dose group, but no histopathological changes were found. A significantly higher number of occurrences of edema in the perivascular region of the brain and vacuolarization in the cortex of dams were observed at all doses. Some significant variations in fetal skeletons, such as a shorter radius and a longer ulna, were observed in both treated groups. A significantly higher number of fetuses showed enlargement in the intermyofibrillar area of the fetal heart in both dose groups. Fetal body weight and length were significantly higher at 100 mg/kg bw/day, and the placenta size (diameter, thickness, and weight) was larger. However, the placenta was significantly smaller in fetuses in the 25 mg/kg bw/day group. At 100 mg/kg bw/day, a lower number of implantations was calculated, and a dose-dependent increase in resorptions was observed from control (4%) to low dose (12%) and was significant in the high-dose group (20%). A LOAEL of 25 mg/kg bw/day was estimated on the basis of the dose-dependent increase in resorptions, edema in the maternal brains, and fetal skeletal variations.

In another developmental study, pregnant Wistar rats (21/dose) were orally administered 0, 0.4, or 1% benzyl benzoate (equivalent to 0, 26, or 646 mg/kg bw/day as determined by the authors, respectively) by diet from GD 1 to PND 20 (ECHA registration dossier 2020c). One group of 14 animals from each dose was sacrificed at GD 20, while another group of 7 animals per dose was kept until PND 21. No clinical signs of toxicity or body weight changes were observed in dams. A decrease in implantation loss was observed in the high-dose group only but was not statistically significant. A non-significant dose-related increase in malformations such as dilation of renal pelvis, bifid apex of heart, submaxilla defect, tongue defect, cleft palate, or heterotaxia in control (1%), low- (1.2%) and high- (8.8%) dose groups was observed. Authors of the study observed a lower body weight in pups from treated dams, but this was not considered adverse by the authors because it was not statistically significant and did not follow a dose-response pattern. No other clinical changes were seen by the authors. A NOAEL of 646 mg/kg bw/day, the highest dose tested, was determined by the authors (ECHA Registration dossier 2020c). In this assessment, a LOAEL of 26 mg/kg bw/day is recommended on the basis of the decrease in body weight in postnatal pups at both doses in the absence of maternal toxicity and the increase in fetal malformations in the absence of maternal toxicity at 646 mg/kg bw/day. When compared with the previous study (Koçkaya and Kılıç 2011), differences in the results may be related to the route of administration.

In an *in vitro* assay, benzyl benzoate was a weak estrogenic competitor to oestradiol but was capable of binding human estrogen receptors ER α and ER β , and increasing the estrogen-responsive reporter gene (ERE-CAT) and endogenous estrogen-responsive pS2 gene in MCF7 cells (Charles and Darbre 2009). Benzyl benzoate was also positive in the proliferation assay in MCF7 cells (Charles and Darbre 2009). The authors of the study concluded that benzyl benzoate is estrogenic to human cells (Charles and Darbre 2009).

Linalool

Linalool was assessed by ECCC and HC as a major component of bois de rose oil, and no health effects of concern were identified. Exposure to bois de rose oil was therefore considered to be of low risk to human health (ECCC, HC 2020).

(3E,6E)-alpha-Farnesene

There are no other empirical health effects data available for (3E,6E)-alpha-farnesene.

The EFSA used beta-myrcene as a representative substance to assess the safety of acyclic terpene hydrocarbons, of which alpha-farnesene is a part (EFSA 2015). A NOAEL of 300 mg/kg bw/day beta-myrcene was determined by ECCC and HC for reproductive and developmental toxicity on the basis of an 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 at 500 mg/kg bw/day in rats (ECCC, HC 2020).

Phytol

There are limited empirical health effects data for phytol. Phytol is an acyclic diterpene alcohol that can be used as a precursor for the manufacture of synthetic forms of vitamin E and vitamin K₁ (NCBI 2019).

Phytol is classified as a tumour promotor by the Chemical Carcinogenesis Research Information System, with an unspecified mode of action in the PubChem database (NCBI 2019). In the Comparative Toxicogenomics Database, phytol interferes with genes linked to liver necrosis, hypertrophy, injury, and neoplasm as well as to hyperplasia and diseases, neoplasms, and interstitial tumour in lungs (CTD 2019).

One group of rats (6/dose) was fed with 2% phytol (approximately equivalent to 1000 mg/kg bw/day) for 40 weeks (Steinberg et al. 1966). Only one animal died at the end of the exposure period. All treated rats showed a lowest body weight. The authors did not describe any findings.

In several studies, mice and rats, males and females, were fed with 0%, 0.5%, or 1% phytol (approximately equivalent to 0, 250, and 750 mg/kg bw/day, respectively) for variable periods of time (from 19 days to 15 months) (Steinberg et al. 1966; Atshaves et al. 2004; Mackie et al. 2009). None of the animals died, but many showed hepatotoxicity effects with hypertrophy and hyperplasia or hepatocyte necrosis with early inflammation in all treated animals.

In a short-term inhalation study, Sprague-Dawley rats (5/sex/dose) were exposed to an average phytol aerosol of 5.5 mg/L for 0 or 30 minutes and 1, 2, 4, or 6 hours per day for 14 consecutive days by nose only (Schwotzer et al. 2021). The authors of the study estimated a dose range of 12.9 mg/kg bw to 155.0 mg/kg bw using a deposition fraction of 10% based on the size of the aerosol. The protocol was unexpectedly terminated on day 2 because of severe clinical signs at all times of exposure and mortality in 4-hour

and 6-hour groups post exposure. All animals showed piloerection, hunched posture, and rapid respiration within the first two days. Animals exposed to phytol for 4 hours and 6 hours demonstrated severely discoloured purple lungs on gross examination. Absolute and relative lung weights were significantly increased at 4 hours and 6 hours. In addition, the respective increase was dose-related. The respiratory tract showed a dose-responsive degeneration and necrosis of epithelium within the nose/turbinates, larynx, and trachea. Pulmonary edema with fibrin, and widespread mixed cell inflammation with abundant macrophages, lymphocytes, and neutrophils were observed in the lungs of the 4- and 6-hour groups. For 0.5-, 1-, and 2-hour exposures, animals showed a mixed cell inflammation in the lungs and a distinct centriacinar distribution. The authors of the study did not assess other systemic effects; however, they estimated a LOAEL of 10.8 mg/kg bw/day for phytol based on the high level of toxicity in lungs and death at higher exposures after 2 days (Shwotzer et al. 2021). Authors of the study recommended further assessment of phytol inhalation exposure because of the lower aerodynamic diameter (0.99 μm), which is an indication of a deep lung delivery, and because the study design was based on the hypothesis of low toxicity.

Phytol was found not to be mutagenic in the Ames assay with *S. typhimurium* strain TA100 with and without metabolic activation and in the Drosophila wing spot test (Choi et al. 1993). However, phytol showed clastogenic effects in the Comet assay with *Allium cepa* (Islam et al. 2017).

Multiple *in vitro* studies showed that not only does phytol have anti-angiogenic and anti-proliferative potential, but it also stops the cell cycle (mitosis) of lung adenocarcinoma cells (Itoh et al. 2018; Sakthivel et al. 2018).

Without further information, phytol is considered to be clastogenic.

Isophytol

Isophytol was reviewed internationally in an OECD Screening Information Data Set (SIDS) Initial Assessment Report, which considered isophytol to be of low toxicity for mammals on the basis of animal data (OECD 2003).

In a short-term study, male and female rats (12/dose/sex) were administered 0, 250, 500, or 1000 mg/kg bw/day isophytol for 28 days, with a 14-day recovery period (OECD 2003). No clinical signs or effects were observed at the low and middle doses. Fur-staining, increased kidney and spleen weights in females, hunched posture, weight loss and pallor, increased body weight in males, and some blood chemistry changes and increased liver weights in males and females were observed at the highest dose (OECD 2003). No histopathological changes were observed, and the majority of changes were no longer apparent after the recovery period (OECD 2003). On the basis of these results, a NOAEL of 500 mg/kg bw/day and a LOAEL of 1000 mg/kg bw/day were identified for isophytol (OECD 2003).

In a reproductive and developmental study, female and male rats were orally administered 0, 250, 500, or 1000 mg/kg bw/day isophytol by gavage for 10 weeks prior to mating in males and for at least 8 weeks in females (2 weeks prior to mating, 3-week gestation, 3-week lactation) (OECD 2003). At the highest dose, females showed an increase in lethargic behaviours, hunched posture, and piloerection. No significant body weight changes were observed. The absolute and relative food consumption of the females in the mid- and high-dose groups was increased during part of the pre-mating and post-mating periods, but the absolute food consumption was decreased during the complete lactation period. Absolute and relative kidney weights were significantly increased in females in the mid- and high-dose groups and only at the highest dose in males with presence of basophilic aggregates and an increase in the incidence of basophile tubules. Dilated renal tubules and general mineralization were observed in all treated animals. In the high-dose group, females showed a decrease in fertility index and conception rate and an increase in dead pups per litter, post-natal losses, and breeding losses. Post-natal losses were also increased in the low- and mid-dose groups (OECD 2003). As these values, with the exception of the high-dose group, were within the historical control range, this finding was considered to be caused by chance and not due to the treatment administered by OECD (OECD 2003). However, these values were not provided in the report by OECD for further review. Survival and general fitness of pups was reduced in the high-dose group. Pups showed pronounced clinical signs such as very small or cold body, little or no milk uptake, and death. On the basis of these results, OECD determined a LOAEL of 250 mg/kg bw/day, the lowest dose tested, for systemic toxicity in kidneys in both sexes, and a NOAEL of 500 mg/kg bw/day for maternal reproductive and developmental effects (OECD 2003).

Isophytol was not genotoxic in the Ames test with *S. typhimurium* strains TA97, TA98, TA100, TA102, TA103, TA1535, and TA1537, with or without metabolic activation (OECD 2003). Isophytol was also negative in the micronucleus assay in mice (OECD 2003).

Nerolidol

Nerolidol has been evaluated by JECFA for use as a food flavouring agent (WHO 2008), which concluded on the basis of the low exposure that this substance presents “no safety concern at current levels of intake when used as a flavouring agent.” Similarly, EFSA concluded that the low estimated level of intake of nerolidol as a flavouring substance presents no safety concern (EFSA 2010). There are limited empirical health effects data for nerolidol.

In a study conducted according to OECD Test Guideline 422, Wistar male and female rats (10/sex/dose) were administered 0, 1 500, 4 000, or 12 000 ppm (equivalent to 0, 100, 300, or 1 000 mg/kg bw/day, respectively) nerolidol by diet for 37 days (before mating and during mating) for males and 58 days for females (before mating, during mating, during pregnancy and lactation) (ECHA Registration dossier 2020d). A decrease in food consumption and body weight was observed in females at 4 000 and 12 000 ppm. Liver weights were increased in both sexes in the high-dose group and in

females in the mid-dose group. Females also presented with central hepatocellular hypertrophy and central fatty change in the mid- and high-dose groups (ECHA Registration dossier 2020d). No effects were observed in parental fertility and reproductive parameters. A decrease in body weight in pups was observed only in the high-dose group and was a secondary effect from maternal toxicity (ECHA Registration dossier 2020d). On the basis of these results, a NOAEL of 1 500 ppm (100 mg/kg bw/day) was determined for liver toxicity in females at 4 000 ppm (300 mg/kg bw/day) (ECHA Registration dossier 2020d).

In an *in vivo* study, nerolidol was clastogenic in peripheral blood and liver cells in the Comet assay and the micronucleus assay from exposed Swiss mice (Pículo et al. 2010). In an *in vitro* study compliant with OECD Test Guideline 480, nerolidol was not mutagenic in gene mutation assay using *Saccharomyces cerevisiae*, but it was highly cytotoxic (Sperotto et al. 2013).

7.3.3 Characterization of risk to human health

The characterization of risk from jasmine oil considers both systemic effects resulting from the sum of all relevant routes of exposure (oral, dermal, inhalation) as well as an inhalation-specific risk.

For systemic exposures, the identified endpoint was an oral reproductive toxicity LOAEL of 250 mg/kg bw/day jasmine extract (the lowest dose tested) in rats (Iqbal et al. 1993). An increase in implantation loss, fetal mortality, and resorption, and a decrease in fertility and progesterone level were observed at 250 mg/kg bw/day and above. This POD was considered relevant for all age groups. From the critical study defined above, jasmine oil can modify the level of some reproductive hormones in adult rats following a short-duration (for example, 5 days) exposure. A dermal absorption factor of 50% was incorporated for dermal exposures.

For the inhalation route, risks were also characterized for site-of-contact effects from a component of jasmine oil (phytol) by comparing per event estimated phytol concentrations in air to 5.5 mg/L, the LOAEL that resulted in phytol-induced inflammation in the lungs and a dose-responsive degeneration and necrosis of the respiratory tract in rats (Schwotzer et al. 2021).

The combined approach is considered protective for both short- and long-term systemic effects, as well as localized effects during the exposure in question. Estimates of daily systemic exposure to jasmine oil for the highest and lowest exposed age groups and resulting MOEs from food flavouring agent, cosmetics, and other products available to consumers are summarized in Table 7-15, and daily systemic exposure estimates of jasmine oil and resulting MOEs from DIY products are summarized in Table 7-16. Estimated per event air concentrations of phytol in jasmine oil and resulting MOEs are summarized in Table 7-17.

Table 7-15. Daily exposure estimates of jasmine oil and resulting MOEs from products available to consumers

Exposure scenario	Systemic exposure (mg/kg bw/day)^a	MOE^b
Food flavouring agent (1 year of age and older)	4.94 x 10 ⁻⁶	>2 000 000
Dermal and inhalation exposures from hair conditioner (wash-off) (30%) (9–13 years to adults)	5.68 x 10 ⁻² (adults) to 6.44 x 10 ⁻² (9–13 years)	3 885 (9–13 years) to 4 400 (adults)
Dermal and inhalation exposures from liquid body cleanser (3%) (all subpopulations)	3.71 x 10 ⁻² (adults) to 0.13 (0–5 months)	1 882 (0–5 months) to 6 736 (adults)
Dermal and inhalation exposures from body moisturizer (3%) (all subpopulations)	2.07 (adults) to 4.78 (0–5 months)	52 (0–5 months) to 121 (adults)
Dermal and inhalation exposures from facial moisturizer/acne treatment (NHP) (1%) (9–13 years to adults)	0.32 (adults) to 0.40 (9–13 years)	626 (9–13 years) to 782 (adults)
Dermal and inhalation exposures from topical treatment cream (NHP) (1%) (9–13 years to adults)	0.11 (adults) to 0.14 (9–13 years)	1 822 (9–13 years) to 2 344 (adults)
Dermal and inhalation exposures from facial sun protection powder (NHP) (0.07%) (adults)	2.2 x 10 ⁻³ (adults)	114 000
Dermal and inhalation exposures from de-stress roll-on (NHP) (0.01%) (adults)	3 x 10 ⁻⁴ (adults)	>800 000
Oral exposure from lipstick (3%) (2–3 years to adults)	1.78 x 10 ⁻² (adults) to 4.40 x 10 ⁻² (2–3 years)	5 682 (2–3 years) to 14 015 (adults)
Dermal and inhalation exposures from body fragrance (82%) (2–3 years to adults)	3.12 (14–18 years) to 9.14 (2–3 years)	27 (2–3 years) to 80 (14–18 years)
Dermal and inhalation exposures from aerosol hair styling product (0.1%) (4–8 years to adults)	1.58 x 10 ⁻³ (14–18 years) to 4.26 x 10 ⁻³ (4–8 years)	58 697 (4–8 years) to 158 079 (14–18 years)
Dermal and inhalation exposures from an antiperspirant/deodorant (2%) (9–13 years to adults)	0.11 (9–13 years) to 0.18 (14–18 years)	1 377 (14–18 years) to 2 341 (9–13 years)
Dermal and inhalation exposures from temporary hair colour (0.1%) (4–8 years to adults)	2.42 x 10 ⁻² (adults) to 7.73 x 10 ⁻² (4–8 years)	3 234 (4–8 years) to 10 348 (adults)
Dermal exposure from sunscreen (NHP) (0.07%) (6–11 months to adults)	7.35 x 10 ⁻² (9–13 years) to 3.32 x 10 ⁻¹ (6–11 months)	752 (6–11 months) to 3 401 (9–13 years)

Exposure scenario	Systemic exposure (mg/kg bw/day)^a	MOE^b
Dermal and inhalation exposure from antiseptic skin cleanser (NHP) (2%) (2–3 years to adults)	0.38 (14–18 years) to 1.09 (2–3 years)	230 (2–3 years) to 657 (14–18 years)
Dermal and inhalation exposure from antiseptic skin cleanser (NHP) (2%) (2–3 years to adults) ^c	5.67 (adults) to 27.2 (2–3 years)	9 (2–3 years) to 44 (adults)
Dermal and inhalation exposures from an aerosol all-purpose cleaner (1%) (adults)	7×10^{-2} (adults)	3 576 (adults)
Dermal and inhalation exposures from liquid all-purpose floor cleaner (1%) (adults)	2.53×10^{-2} (adults)	9 896 (adults)
Dermal, inhalation, and incidental oral (hand-to-mouth) exposures from post-application exposure to cleaned floor (1 year)	1.16×10^{-2} (1 year)	21 567 (1 year)
Inhalation exposure from aerosol laundry conditioner (5%) (adults)	2.45×10^{-2} (adults)	10 210 (adults)
Dermal and inhalation exposures from machine washing laundry (liquid) (mix, load, hanging, migration from clothes) (5%) (adults)	1.86×10^{-1} (adults)	1 341 (adults)
Dermal and incidental oral exposures (1 year only) from migration from machine-washed clothes (5%) (all subpopulations except adults)	5.54×10^{-3} (14–18 years) to 9.28×10^{-3} (0–6 months)	26 950 (0–6 months) to 45 134 (14–18 years)

^a Exposure scenario parameters and calculations for jasmine oil are outlined in Appendix A. Dermal absorption was assumed to be 50%.

^b The MOEs were calculated using the critical effect level (LOAEL = 250 mg/kg bw/day) based on female reproductive toxicity.

^c For situations of public health concern, the use of hand sanitizers among the general population may increase up to 25 uses per day (personal use by adults, increased use by children in schools and child care facilities) (RIVM 2021a).

Table 7-16. Daily exposure estimates of jasmine oil and resulting MOEs for DIY products

Exposure scenario	Systemic exposure (mg/kg bw/day)^a	MOE^b
Systemic exposure by the dermal route (for the 9–13 years to adults only) and by inhalation route from DIY aromatic diffuser (100%) (all subpopulations)	1.16 (adults) to 1.97 (14–18 years)	127 (9–13 years) to 216 (adults)

Exposure scenario	Systemic exposure (mg/kg bw/day)^a	MOE^b
Dermal and inhalation exposures from DIY massage oil (3%) (all subpopulations)	6.89 x 10 ⁻¹ (adults) to 4.35 (0–5 months)	57 (0–5 months) to 363 (adults)
Dermal and inhalation exposures from DIY bath oil product (100%) (9–13 years to adults)	1.56 x 10 ⁻¹ (adults) to 2.51 x 10 ⁻¹ (9–13 years)	997 (9–13 years) to 1 606 (adults)
Dermal and inhalation exposures from DIY body moisturizer (3%) (all subpopulations)	2.07 (adults) to 4.78 (0–5 months)	52 (0–5 months) to 121 (adults)
Dermal and inhalation exposures from DIY facial steamer/mist ^c (100%) (4–8 years to adults)	1.19 (adults) to 3.47 (4–8 years)	72 (4–8 years) to 210 (adults)
Dermal and inhalation exposures from DIY facial steamer for bystander (1 year only) (100%)	5.26 x 10 ⁻¹	475

^a Exposure scenario parameters and calculations for jasmine oil are outlined in Appendix A. Dermal absorption was assumed to be 50%.

^b The MOEs were calculated using the critical effect level (LOAEL = 250 mg/kg bw/day) based on female reproductive toxicity.

^c After a total of 4 hours of exposure; once the device is turned off after 20 minutes of use, it is assumed that the person remains in the room for 3 hours and 40 minutes.

Table 7-17. Estimated per event air concentrations of phytol in jasmine oil and resulting MOEs

Product scenario	Per event air concentration (mg/m³)^a	MOE^b
Air freshener (100%) (all subpopulations)	3.2	>1 700 (all subpopulations)
Aerosol hair styling product (0.1%) (4–8 years to adults)	2.70 x 10 ⁻³ (18 years and below) to 3.10 x 10 ⁻³ (adults)	>1 700 000 (adults) >2 000 000 (18 years and below)
Aerosol laundry conditioner (5%) (adults)	5.50 x 10 ⁻³	>1 000 000 (adults)
Aerosol all-purpose cleaner (1%) (adults)	1.50 x 10 ⁻³	>3 000 000 (adults)
Liquid all-purpose cleaner (1%) (adults)	1.72 x 10 ⁻⁷	>32 100 000 000 (adults)

^a Per event air concentrations were adjusted by 50% for the maximum amount of components with toxicity in jasmine oil.

^b The MOEs were calculated using the critical effect level (LOAEL = 5.5 mg/L) based on lung toxicity in rats after 2 days of exposure to phytol.

The MOEs for jasmine oil from food (based on its potential use as a flavouring agent), hair conditioner, body cleanser, topical treatment cream (NHP), facial sun protection powder (NHP), de-stress roll-on (NHP), lipstick, hair styling product, antiperspirant/deodorant, temporary hair colour, and sunscreen (2 years of age and

older) (NHP) are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk.

The use of jasmine oil in an aerosol all-purpose cleaner, all-purpose floor cleaner, and a liquid laundry detergent are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk.

In addition, the MOEs for jasmine oil from its uses in a DIY bath oil product are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk.

The MOEs between the critical effect levels and the estimates of daily exposure from body moisturizer, body fragrance, facial moisturizer/acne treatment (NHP), sunscreen (1-year-olds and 6- to 11-month-olds) (NHP), and antiseptic skin cleanser (NHP) are below 1000, which account for uncertainties with respect to interspecies extrapolation, intraspecies extrapolation, the POD, and the adequacy of the database and are considered potentially inadequate.

In addition, the use of jasmine oil in DIY products such as aromatic diffuser, massage oil, body moisturizer, or a facial steamer are below 1000, which accounts for uncertainties with respect to interspecies extrapolation, intraspecies extrapolation, the POD, and the adequacy of the database and is considered potentially inadequate to address uncertainties in the health effect and exposure data used to characterize risk.

It should be noted that a component of jasmine oil, benzyl benzoate, exhibited developmental effects in rats, such as enlargement in the intermyofibrillar area of the fetal heart and skeleton variations at the lowest dose tested (25 mg/kg/day), and was classified as a potential estrogenic substance for human cells in an *in vitro* study (Charles and Darbre 2009). If the jasmine oil present in products available to consumers contains greater than 10% benzyl benzoate, the current assessment may not be sufficiently protective.

The MOEs between the critical effect levels and the per event air concentration estimates from air freshener, aerosol hair styling product, aerosol laundry conditioner, aerosol all-purpose cleaner, and liquid all-purpose cleaner are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk.

7.3.4 Uncertainties in evaluation of risk to human health

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

Table 7-18. Sources of uncertainties in the risk characterization of phenylpropanoids subgroup 1

Key source of uncertainty	Impact
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There is a degree of uncertainty associated with the dermal absorption factor used for jasmine oil, considering the <i>in vivo</i> dermal absorption results for benzyl benzoate and benzyl acetate.	+/-
The upper concentration of jasmine oil in sunscreen and antiseptic skin cleanser are conservative estimates. In the absence of any additional information, the concentration in sunscreen is based on the maximum amount of jasmine oil diluted in water, and the concentration in antiseptic skin cleanser is based on the maximum concentration of other ingredients in the product (SDS 2014b).	+
Jasmine oil may be used in hand sanitizers. There is uncertainty regarding the duration of increased hand sanitizer use that may occur in a situation of public health concern.	+/-
There are no studies via the dermal and inhalation routes.	+/-
No suitable studies were identified for dermal or inhalation exposure; therefore, route-to-route extrapolation from an oral study was used to determine systemic exposure.	+/-
Jasmine oil was considered to be a representative for perfumes and essences of jasmin in the absence of compositional information.	+/-
A component of jasmine oil, benzyl benzoate, exhibited developmental effects in rats at the lowest dose tested (25 mg/kg bw/day). If the jasmine oil present in products available to consumers contains greater than 10% benzyl benzoate, the current assessment may not be sufficiently protective.	-

+ = uncertainty with potential to cause overestimation of exposure/risk; - = uncertainty with potential to cause underestimation of exposure/risk; +/- = unknown potential to cause over- or underestimation of risk. The achieved margins of exposure were considered adequate to address uncertainties in the exposure and hazard databases.

7.4 Violet oil

7.4.1 Exposure assessment

Environmental media

Given that violet oil was not reported as being manufactured or imported into Canada above the reporting threshold of 100 kg (Environment Canada 2013), exposure to this substance from environmental media is not expected. No reports of monitoring for violet oil in environmental media in Canada or elsewhere were identified.

Food

No definitive information is available concerning the potential use of violet oil as a flavouring agent in foods sold in Canada. However, since violet oil is identified as a food flavouring agent internationally, it is possible that this substance is present as a flavouring agent in foods sold in Canada.

The Fenaroli's Handbook of Flavour Ingredients reports the "individual" consumption intake of this substance from its use as a food flavouring agent. Individual consumption

intakes are a per capita estimate of intake based on a MSDI that is based on production volumes reported by the food industry (NAS 1989 as cited in Burdock 2010).

In the absence of data on the actual use, if any, of violet oil as a food flavouring agent in Canada, the per capita intake estimate for the US population of $1.33 \times 10^{-1} \mu\text{g}/\text{kg bw}/\text{day}$ reported in Fenaroli's Handbook of Flavour Ingredients (Burdock 2010) is an acceptable estimate of possible Canadian dietary exposure of the general population 1 year of age and older to this substance from its potential use as a food flavouring agent (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced).

Exposure from natural occurrence in foods

No definitive information is available concerning the natural occurrence of violet oil in foods. However, dietary exposure to this substance, if any, is expected from its natural presence in foods (Nijssen et al. 2018).

Products available to consumers

Violet oil is present in products available to consumers. Based on the health effects assessment of violet oil (section 7.4.2), the inhalation and oral routes of exposure are considered to be the relevant routes for risk characterization, including for dermally applied products available to consumers. The selected sentinel cosmetic scenarios represented the highest exposures, relative to other dermally applied cosmetics as well as NHPs where violet oil is used as an NMI, based on identified products reported to contain this substance. To evaluate the potential for exposure to violet oil from cosmetics applied by the dermal route, sentinel scenarios were selected based on a combination of use frequencies and reported concentrations of violet oil in these products. The selected sentinel scenarios represented the highest exposures, relative to other dermally applied cosmetics and based on identified products reported to contain this substance. Exposure to violet oil from the use of eye moisturizer, hair conditioner, facial cleanser, body moisturizer, and massage oil, and as a body fragrance were considered to be the sentinel scenarios for dermal applications (personal communication, email from the Consumer and Hazardous Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2017; unreferenced).

In addition, the use of 100% violet oil in DIY products such as aromatic diffuser, a bath oil product, body moisturizer, and a facial steamer was also assessed. It is reported that body products are typically diluted to concentrations of 1%–4% (Tisserand Institute 2021). On the basis of this information, the maximum concentration of violet oil in DIY body moisturizer was assumed to be 3%. Although the upper concentration reported for massage oil containing violet oil was 100%, massage oils are typically diluted prior to use. Therefore, the maximum concentration of violet oil in a DIY massage oil was assumed in RIVM (2006) to be 3%, but this scenario is covered by a consumer product massage oil at 10% (personal communication, email from the Consumer and

Hazardous Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2017; unreferenced).

Furthermore, violet oil is present in a lipstick product. Exposure by the oral route from the use of a lipstick was quantified (personal communication, email from the Consumer and Hazardous Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2017; unreferenced).

The product amount available for inhalation via evaporation was adjusted by 80% to account for an estimated 20% retained via the dermal route. The 20% factor was based on *in vitro* human dermal absorption studies for geraniol, citronellol, linalool, and citral (Gilpin et al. 2010; ECHA Registration dossier 2018; Charles River 2019). The physical-chemical properties of 2,6-nonadienal, one of the main components of violet oil, are similar to those of the Terpenes and Terpenoids – Acyclic, Monocyclic, and Bicyclic Monoterpenes Group. The molecular weight, vapour pressure, and log K_{ow} of 2,6-nonadienal are 138.21 g/mol, 31 Pa, and 2.84, respectively. These values are similar to those of geraniol, citronellol, linalool, and citral, which have molecular weights ranging from 152 g/mol to 156.27 g/mol, vapour pressures ranging from 4 Pa to 21 Pa, and log K_{ow} values ranging from 2.9 to 3.5. For body moisturizer, since the product amount for inhalation was adjusted for the exposed surface area, and this value was less than 80% of the product amount, no further adjustment was made to the product amount; for hair conditioner (leave-on), only the product amount in contact with the scalp was considered available for dermal retention, and the total amount of product on the hair was considered to be potentially available for evaporation.

Exposure estimates for the lowest and highest exposed age groups from products available to consumers are summarized in Table 7-19. In addition, exposure estimates for the lowest and highest exposed age groups from DIY products are summarized in Table 7-20.

Table 7-19. Estimated daily exposures from products available to consumers for violet oil

Product scenario	% in product	Route of exposure	Exposure range (mg/kg bw/day) ^a
Eye moisturizer	100%	Inhalation	6.98 x 10 ⁻³ (adults) to 8.78 x 10 ⁻³ (14–18 years)
Hair conditioner (leave-on)	100%	Inhalation	1.82 x 10 ⁻² (adults) to 4.89 x 10 ⁻² (2–3 years)
Facial cleanser	30%	Inhalation	9.12 x 10 ⁻³ (14–18 years) to 1.52 x 10 ⁻³ (adults)
Body moisturizer	10%	Inhalation	1.45 x 10 ⁻² (0–5 months) to 3.14 x 10 ⁻² (9–13 years)
Massage oil	10%	Inhalation	4.26 x 10 ⁻² (adults) to 88.43 x 10 ⁻² (1 year)
Lipstick	10%	Oral	1.13 x 10 ⁻² (adults) to 2.79 x 10 ⁻² (2–3 years)

Body fragrance	10%	Inhalation	2.44 x 10 ⁻³ (adults) to 4.31 x 10 ⁻³ (2–3 years)
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^a Only the lowest to highest exposed age groups are presented. Exposures were adjusted by 19% to account for the maximum amount of 2,6-nonadienal in violet oil, assuming that 80% of the applied dose was available for evaporation. See Appendix A for calculation details.

Table 7-20. Estimated daily exposures from DIY products for violet oil

Product scenario	% in product	Route of exposure	Exposure range (mg/kg bw/day) ^a
Aromatic diffuser	100%	Inhalation	1.56 x 10 ⁻¹ (adults) to 3.73 x 10 ⁻¹ (1 year)
Bath oil product	100%	Inhalation	2.85 x 10 ⁻² (adults) to 4.56 x 10 ⁻² (9–13 years)
Body moisturizer	3%	Inhalation	4.84 x 10 ⁻³ (0-5 months) to 1.05 x 10 ⁻³ (9–13 years)
Facial steamer	100%	Inhalation	0.05–0.02 ^b (adults) 0.13–0.06 ^b (4–8 years)
Facial steamer - bystander exposure (1 year only)	100%	Inhalation	0.10

^a Only the lowest to highest exposed age groups are presented. Exposures were adjusted by 19% to account for the maximum amount of 2,6-nonadienal in violet oil, assuming that 80% of the applied dose was available for evaporation. See Appendix B for calculation details.

^b After a total of 4 hours of exposure; once the device is turned off after 20 minutes of use, it is assumed that the person remains in the room for 3 hours and 40 minutes.

7.4.2 Health effects assessment

There are no international assessments or health effects data available for violet oil.

The only health effects studies available on violet leaf oil showed no irritation, sensitization, or phototoxicity when the substance was dermally tested on animals and human volunteers at 2% in petrolatum. They also indicated anti-inflammatory effects in acute and subacute experiments (Opdyke 1976).

In order to inform the health effects assessment, the hazard information available for the main components of violet oil—2,6-nonadienal (5%–19%), linoleic acid (0%–58%), palmitic acid (0%–17%), and 1-octadecene (0%–11%)—were considered.

2,6-Nonadienal

There are no subchronic, chronic, reproductive/developmental, or carcinogenicity animal studies identified in the literature for 2-trans-6-cis-nonadienal.

In the Ames test with *S. typhimurium* strain TA100, no increase in revertants was observed, with and without metabolic activation (Eder et al. 1992). However, 2,6-

nonadienal significantly increased the number of sister chromatid exchanges in human blood lymphocyte and Namalva cell cultures (Dittberner et al. 1995) and induced chromosomal aberrations in Namalva cells but not in lymphocytes (Dittberner et al. 1995). A significant increase in the number of aneuploidy metaphases was noted after 2,6-nonadienal treatment (Dittberner et al. 1995). Additionally, 2,6-nonadienal induced an increase in the frequency of micronuclei in human blood lymphocyte and Namalva cells in a concentration-dependent manner (Dittberner et al. 1995). With fluorescence *in situ* hybridization, both Namalva cells and human lymphocytes showed a significant increase in enhanced frequencies of centromere-positive micronuclei, which generally result from impaired function of the mitotic spindle, and therefore can be classified as aneugenic effects (Dittberner et al. 1995). Without further information, 2,6-nonadienal may be considered to be aneugenic.

In the absence of hazard data for 2,6-nonadienal, a read-across approach was taken, and hazard information on the read-across analogue, 2,4-hexadienal, was used to inform the health effects assessment.

Both 2,6-nonadienal and 2,4-hexadienal are alpha, beta-unsaturated aldehydes. They are structurally similar, comprising of an aliphatic hydrocarbon chain with three double bonds and one carbonyl group. The only structural difference between the two substances is that 2,6-nonadienal (molecular formula: C₉H₁₄O) has a longer chain length than 2,4-hexadienal (molecular formula: C₆H₈O). The target and analogue are both naturally occurring substances in food, have been identified for use as flavouring ingredients in the food industry, and are endogenously produced from lipid peroxidation products in the body (Adams et al. 2008). 2,6-nonadienal and 2,4-hexadienal have comparable physical-chemical properties, and both have structural features associated with the potential to be highly reactive and interact with biological macromolecules such as DNA. They have the same structural alerts on QSAR Toolbox version 4.2 (OECD 2016), including DNA and protein binding alerts, *in vitro* and *in vivo* mutagenicity, and skin sensitization, making them potentially toxic and capable of modifying cellular processes.

In their US NTP report, the authors concluded that 2,4-hexadienal showed clear evidence of carcinogenic activity in male and female F344/N rats and male and female B6C3F1 mice on the basis of increased incidences of squamous cell neoplasms in the forestomach (NTP 2003). The IARC classified 2,4-hexadienal as possibly carcinogenic to humans (group 2B) based on sufficient evidence for carcinogenicity in experimental animals and the absence of hazard data in humans (IARC 2013). Genotoxicity evaluation of 2,4-hexadienal showed that it was not mutagenic when evaluated by the EFSA Expert Panel (EFSA 2018). JECFA concluded that the neoplasms of the forestomach were caused by non-genotoxic mechanisms such as the irritating effects of prolonged exposure to 2,4-hexadienal administered daily at the site of first contact (forestomach) by gavage and were not a systemic effect induced by the chemical (Nyska et al 2001; Chan et al. 2003; WHO 2004). JECFA also questioned the relevance of the induction of these tumours in rodents to cancer in humans, considering the exposure conditions used in the NTP studies (NTP 2003; WHO 2004). Moreover, the

carcinogenic effect was only observed in animals exposed to high doses of 2,4-hexadienal for two years (NTP 2003).

Rats (5/sex/dose) were administered 0, 0.75, or 7.5 mg/kg bw/day 2,4-hexadienal in corn oil via gavage 6 days a week for 14 days (WHO 2004; Adams et al. 2008). No treatment-related effects were observed on clinical signs, hematology, or histopathology. The study authors established a no-observed-effects level (NOEL) of 7.5 mg/kg bw/day, the highest dose tested (WHO 2004; Adams et al. 2008).

F344/N rats (24/sex/dose) were orally administered 0 or 2.23 mg/kg bw/day 2,4-hexadienal in the diet, 7 days a week for 13 weeks (WHO 2004; Adams et al. 2008). There were no treatment-related effects on body weights or histopathology at necropsy. The authors reported a NOEL of 2.23 mg/kg bw/day, the highest dose tested (WHO 2004; Adams et al. 2008).

In a dose-range finding study, groups of male and female Fischer 344/N rats and B6C3F1 mice (5/sex/dose) were administered 2,4-hexadienal in corn oil by gavage at doses of 0, 3, 9, 27, 80, or 240 mg/kg bw/day, 5 days a week for 16 days (NTP 2003). In rats given the highest dose, mortality was observed in three males and three females before the end of the study. Rats administered 240 mg/kg bw/day had significantly lower body weight gain compared with the controls. Liver weights of female rats given the high dose were significantly greater than those of the controls (the study authors did not mention the presence of histopathological correlates). Clinical signs at the highest dose included diarrhea, ataxia, lethargy, and nasal/eye discharge in male rats, and lethargy, paleness, and abnormal breathing in female rats (NTP 2003). Gross pathological evaluation revealed necrosis and ulceration of the forestomach in most rats of both sexes at 240 mg/kg bw/day, and mild to moderate epithelial hyperplasia of the forestomach at 80 mg/kg bw/day (NTP 2003). No forestomach effect was seen in rats microscopically at 27 mg/kg bw/day. In mice, one male and one female died at the highest dose before the end of the study, and clinical signs included lethargy and ruffled fur. Marked ulceration and necrosis of the forestomach were reported in all mice at 240 mg/kg bw/day. At 80 mg/kg bw/day, there was minimal to mild epithelial hyperplasia and hyperkeratosis, but no forestomach effects were reported at lower doses in mice (NTP 2003).

In a short-term study, groups of F344/N rats (10/sex/dose) were administered 2,4-hexadienal in corn oil by gavage at doses of 0, 7.5, 15, 30, 60, or 120 mg/kg bw/day, 5 days per week for 14 weeks (NTP 2003). All animals survived until the end of treatment. Final mean body weights and body weight gains were decreased at 30, 60, and 120 mg/kg bw/day in males only, compared with the controls (NTP 2003). At the highest dose, incidences of epithelial hyperplasia, degeneration, and chronic active inflammation of the forestomach in males and females as well as incidences of nasal atrophy, osteofibrosis, and exudate in males were significantly increased (NTP 2003). In contrast to male rats, nasal lesions in females were limited to acute necrosis in one animal at 60 mg/kg bw/day and two animals at 120 mg/kg bw/day (NTP 2003).

In another short-term study, B6C3F1 male and female mice (10/sex/dose) were orally administered 2,4-hexadienal in corn oil by gavage at doses of 0, 7.5, 15, 30, 60, or 120 mg/kg bw/day, 5 days per week for 14 weeks (NTP 2003). Treatment did not affect survival or body weight gain in either sex at any dose level. Absolute and relative kidney weights were increased at 60 and 120 mg/kg bw/day (males only), absolute and relative liver weights were increased at 60 mg/kg bw/day (both sexes), and relative liver weights of females in all dose groups were increased compared to the controls. An increase in the incidence of minimal to mild epithelial hyperplasia of the forestomach (in the absence of inflammation or basal cell proliferation) was observed only in females at 120 mg/kg bw/day. The incidences of minimal to mild olfactory epithelial necrosis were significantly increased in both sexes at 120 mg/kg bw/day, whereas the incidence of olfactory epithelial atrophy was significantly increased only in males at this dose (NTP 2003).

In a carcinogenicity study, groups of F344/N male and female rats (50/sex/dose) were administered 2,4-hexadienal in corn oil by gavage at doses of 0, 22.5, 45, or 90 mg/kg bw/day, five days per week for two years (NTP 2003). Survival was not affected by the treatment. The chemical induced significant increases in the incidence of squamous cell papilloma of the forestomach in the 45 and 90 mg/kg bw/day groups in both sexes. No other significant treatment-related tumours were observed in the treated animals. The incidence of epithelial hyperplasia in the forestomach (focally extensive to diffuse thickenings of all layers of the squamous epithelium, which is considered a potential precursor lesion to neoplasia in the forestomach) was significantly increased in all dose groups for both sexes, with mild to moderate severity at 45 and 90 mg/kg bw/day, respectively. At the highest dose, males showed an increase in inflammation and cysts in the forestomach. These were interpreted by the authors to be the results of downward growths of benign hyperplastic epithelium (NTP 2003). A LOAEL of 22.5 mg/kg bw/day was identified based on the presence of a dose-response of epithelial hyperplasia in the forestomach at all doses in both sexes in rats. This critical effect level was adjusted by multiplying by 5/7 to adjust for the exposure frequency (animals were exposed for 5 days per week), resulting in a LOAEL of 16.1 mg/kg bw/day.

In a carcinogenicity study, groups of B6C3F1 male and female mice (50/sex/dose) were administered 2,4-hexadienal in corn oil by gavage at doses of 0, 30, 60, or 120 mg/kg bw/day, five days per week for two years (NTP 2003). Survival was not affected by the treatment. The incidences of squamous cell papilloma and squamous cell papilloma or carcinoma (combined) in the forestomach were significantly greater in males at 120 mg/kg bw/day and in females at 60 and 120 mg/kg bw/day. The incidence of forestomach squamous cell carcinoma alone was significantly increased in females only at the high dose. Non-neoplastic lesions of the forestomach, consisting of squamous epithelial hyperplasia, were increased in females at 60 mg/kg bw/day and in both sexes at 120 mg/kg bw/day, and the incidence of ulcers was increased in males at 120 mg/kg bw/day. Two male mice in the high-dose group exhibited squamous cell carcinoma of the tongue. The study authors justified this result by explaining that the chemical on the end of the gavage needle may have been deposited in the oral cavity during the gavage

procedure or that some regurgitation of gavaged material may have occurred (NTP 2003).

Genotoxicity evaluation of 2,4-hexadienal showed that it was not mutagenic in the Ames test in *S. typhimurium* strains TA102 (Marnett et al. 1985), TA98, TA1535 (Florin et al. 1980; NTP 2003), TA100, and TA1537 (Florin et al. 1980), with or without metabolic activation. However, other studies using the Ames test showed that 2,4-hexadienal was positive with *S. typhimurium* strains TA100 (Eder et al. 1992; NTP 2003) and TA104 (Marnett et al. 1985). 2,4-Hexadienal showed weak but statistically significant positive results in an *in vitro* gene mutation assay at the hypoxanthine-guanine phosphoribosyl transferase locus in mouse lymphoma L5178Y cell line with metabolic activation (EFSA 2018). However, the study authors considered 2,4-hexadienal to be non-mutagenic since the results could not be compared against historical control values and could not be confirmed in other experiments (EFSA 2018). No mutagenicity was reported in the SOS chromotest with *Escherichia coli* (*E. coli*) strains PQ37 and PQ243 incubated with 2,4-hexadienal (Eder et al. 1992). However, 2,4-hexadienal induced DNA strand breaks in an alkaline elution assay using L1210 mouse leukemia cells (Eder et al. 1993). *In vivo* assays showed inconclusive results in micronucleus assays in bone marrow polychromatic erythrocytes of male mice and male rats administered 2,4-hexadienal intraperitoneally at doses ranging from 40 mg/kg bw/day to 160 mg/kg bw/day (mice) and from 50 mg/kg bw/day to 200 mg/kg bw/day (rats) (NTP 2003). In these assays, the trend analysis of the response over the dose ranges was significant; however, none of the mean values for the individual groups of treated animals differed significantly from the control group value (NTP 2003). Negative results were reported for micronucleus assays of peripheral blood normochromatic (mature) erythrocytes of male and female mice exposed to 2,4-hexadienal (7.5 mg/kg bw/day to 120 mg/kg bw/day) via gavage for 14 weeks (NTP 2003). Similarly, 2,4-hexadienal tested negative for potential clastogenic or aneugenic effect in an *in vivo* micronucleus assay with scoring in bone marrow cells and peripheral blood reticulocytes of male rats by oral gavage or intraperitoneally (EFSA 2018). 2,4-Hexadienal did not show any significant increase in cII mutant frequency when tested in a transgenic rodent gene mutation assay for its potential to induce gene mutations in mice (EFSA 2018). In accordance with the EFSA Panel conclusions, the concern for genotoxicity can be ruled out based on the results from the comprehensive battery of *in vitro* and *in vivo* tests on 2,4-hexadienal.

Linoleic acid

9,12-Octadecadienoic acid, an omega-6 fatty acid also known as linoleic acid, is a polyunsaturated fatty acid that is naturally present in vegetable oils (Whelan and Fritsche 2013). Linoleic acid is the main component of evening primrose oil (70% to 77% of the oil), which was evaluated by ECCC and HC as a substance in the Fatty Acids and Derivatives Group (ECCC, HC 2018c). The available information indicates that evening primrose oil is considered to be of low hazard potential, and risk to human health is considered to be low (ECCC, HC 2018c). The US FDA has confirmed GRAS status for linoleic acid as a direct food substance used as a food flavouring agent or adjuvant (US FDA 2018). In 1998 and 2002, JECFA evaluated linoleic acid as a single

substance and as a mixture combined with linolenic acid and concluded that it presented no safety concern at current levels of intake when used as a food flavouring agent (WHO 2019). NICNAS identified linoleic acid as being of low concern to human health (NICNAS 2017a).

Limited data are available on the toxicity of linoleic acid. In an OECD SIDS Initial Assessment Profile, linoleic acid was evaluated among other fatty acids including palmitic acid, another major component of violet oil (OECD 2014). Linoleic acid and palmitic acid were not identified as possessing properties indicating a hazard to human health for systemic health effects (OECD 2014).

In a study following the Chernoff/Kavlock Developmental Toxicity Screen, groups of female mice (26-30/dose) were administered 10 g/kg bw/day of linoleic acid via oral gavage on GDs 8 to 12 (OECD 2014). No reproductive or developmental effects were observed at this dose (OECD 2014).

In addition, no adverse findings were noted in a repeated-dose oral toxicity study in which a group of twenty male rats were administered linoleic acid in the diet at a dose of 1.5% (~467 mg/kg bw/day to 1970 mg/kg bw/day) for 36 weeks (OECD 2014).

Linoleic acid was not mutagenic when tested in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA97 in the presence and absence of metabolic activation (OECD 2014).

Palmitic acid

JECFA evaluated palmitic acid and concluded that it presented no safety concern at current levels of intake when used as a food flavouring agent (WHO 1999). NICNAS identified palmitic acid as being of low concern to human health (NICNAS 2017b).

A safety assessment of the Oleic Acid Group including palmitic acid by the CIR Expert Panel was published in 1987, with a conclusion that these ingredients are safe in present practices of use and concentration in cosmetics (CIR 1987). A re-evaluation of this group demonstrated no toxicity to reproductive and developmental physiology by palmitic acid (CIR 2006). Palmitic acid was evaluated by the RIFM in a fragrance ingredient safety assessment using a TTC approach for repeated-dose and reproductive toxicity endpoints, and the expert panel concluded that palmitic acid is safe to use at current levels of exposure (Api et al. 2019).

1-Octadecene

The OECD SIDS published an Initial Assessment Profile on higher olefins, including 1-octadecene, and used a category/analogue approach to assess them (OECD 2004).

In a reproduction and developmental toxicity screening test, male and female rats (12/sex/dose) were administered 0, 100, 500, or 1000 mg/kg bw/day of a test substance

containing a mix of octadecene isomers (% of the test substance is unknown in the mix) by oral gavage for two weeks prior to mating and during mating (males and females), four weeks following mating for males, and during gestation and following parturition for females (OECD 2004). Based on the absence of clinical, reproductive, and developmental effects, a NOAEL of 1000 mg/kg bw/day, the highest dose tested, was identified by the study authors (OECD 2004).

The expert panel on this assessment concluded that, based on the weight of evidence from toxicity studies with olefins, category members, including 1-octadecene, are currently of low priority for further work (OECD 2004).

7.4.3 Characterization of risk to human health

2,6-Nonadienal was determined to be the main component of toxicological significance for violet oil. An adjusted LOAEL of 16.1 mg/kg bw/day was identified for 2,4-hexadienal (analogue of 2,6-nonadienal) based on the presence of a dose-dependent response in epithelial hyperplasia in the forestomach at all doses in both sexes in the 2-year carcinogenicity study in rats (NTP 2003). This was considered applicable for both the oral and inhalation routes of exposure. However, these effects were not considered relevant for the characterization of risks from the dermal route. Given the lack of any other suitable POD, dermal exposures were not considered further in this assessment.

The EFSA (2018) and WHO (2004) reported that non-genotoxic mechanisms have been proposed for the possible carcinogenicity of 2,4-hexadienal. The NTP (2003) stated that the development of tumours following administration of 2,4-hexadienal was observed in rats exposed to doses ≥ 45 mg/kg bw/day (females) and in mice exposed to doses of ≥ 60 mg/kg bw/day (females) and 120 mg/kg bw/day (males). No difference in neoplastic effects was observed between the control group and the lowest dose group, 22.5 mg/kg bw/day (NTP 2003). Therefore, the non-carcinogenic LOAEL of 16.1 mg/kg bw/day from 2,4-hexadienal used to characterize the risk for violet oil is considered sufficiently protective.

Daily exposure estimates for the highest and lowest exposed age groups and resulting MOEs are summarized in Table 7-21 for food flavouring agent and products available to consumers. In addition, daily estimates for the highest and lowest age groups and resulting MOEs are summarized in Table 7-22 for DIY products.

Table 7-21. Daily exposure estimates and resulting MOEs for violet oil from food and products available to consumers

Exposure scenario	Exposure range (mg/kg bw/day) ^a	MOE range ^b
Food flavouring agent (1 year and older)	2.52×10^{-5}	>630 000
Inhalation exposure from eye moisturizer (100%) (14–18 years to adults)	6.98×10^{-3} (adults) to 8.78×10^{-3} (14–18 years)	1836 (14–18 years) to 2307 (adults)

Exposure scenario	Exposure range (mg/kg bw/day) ^a	MOE range ^b
Inhalation exposure from hair conditioner (leave-on) (100%) (2–3 years to adults)	1.82 x 10 ⁻² (adults) to 4.89 x 10 ⁻² (2–3 years)	329 (2–3 years) to 884 (adults)
Inhalation exposure from facial cleanser (30%) (9–13 years to adults)	9.12 x 10 ⁻³ (14–18 years) to 1.52 x 10 ⁻³ (adults)	1060 (adults) to 1756 (14–18 years)
Inhalation exposure from body moisturizer (10%) (all subpopulations)	1.45 x 10 ⁻² (0–5 months) to 3.14 x 10 ⁻² (9–13 years)	512 (9–13 years) to 1110 (0–5 months)
Inhalation exposure from massage oil (10%) (all subpopulations)	44.26 x 10 ⁻² (adults) to 88.43 x 10 ⁻² (1 year)	191 (1 year) to 378 (adults)
Oral exposure from lipstick (10%) (2–3 years to adults)	1.13 x 10 ⁻² (adult) to 2.79 x 10 ⁻² (2–3 years)	578 (2–3 years) to 1425 (adults)
Inhalation exposure from body fragrance (10%) (2–3 years to adults)	2.44 x 10 ⁻³ (adults) to 4.31 x 10 ⁻³ (2–3 years)	3734 (2–3 years) to 6592 (adults)

^a Exposure estimates were adjusted by 19% for the maximum amount of 2,6-nonadienal present in violet oil, assuming that 80% of the applied dose was available for evaporation (except for the exposure from food flavouring agent). Details are available in Appendix A.

^b The MOEs were calculated using an adjusted non-carcinogenic LOAEL of 16.1 mg/kg bw/day for the read-across analogue 2,4-hexadienal, based on the presence of mild to moderate forestomach epithelial hyperplasia at all doses in both sexes in the 2-year carcinogenicity study in rats.

Table 7-22. Daily exposure estimates and resulting MOEs for violet oil from DIY products

Exposure scenario	Exposure range (mg/kg bw/day) ^a	MOE range ^b
Inhalation exposure from DIY aromatic diffuser (100%) (all subpopulations)	1.56 x 10 ⁻¹ (adults) to 3.73 x 10 ⁻¹ (1 year)	43 (1 year) to 154 (adults)
Inhalation exposure from DIY bath oil product (100%) (9–13 years to adults)	2.85 x 10 ⁻² (adults) to 4.56 x 10 ⁻² (9–13 years)	353 (9–13 years) to 565 (adults)
Inhalation exposure from DIY body moisturizer (3%) (all subpopulations)	4.84 x 10 ⁻³ (0–5 months) to 1.05 x 10 ⁻³ (9–13 years)	1536 (9–13 years) to 3330 (0–5 months)
Inhalation exposure from DIY facial steamer/mist ^c (100%) (4–8 years to adults)	0.08 (adults) to 0.2 (4–8 years)	82 (4–8 years) to 198 (adults)
Inhalation exposures from DIY facial steamer for bystander (100%) (1 year only)	0.10	168

^a Exposure estimates were adjusted by 19% for the maximum amount of violet oil aldehyde present in violet oil, assuming that 80% of the applied dose was available for evaporation (except for the exposure from food flavouring agent). Details are available in Appendix B.

^b The MOEs were calculated using an adjusted non-carcinogenic LOAEL of 16.1 mg/kg bw/day for the read-across analogue 2,4-hexadienal, based on the presence of mild to moderate forestomach epithelial hyperplasia at all doses in both sexes in the 2-year carcinogenicity study in rats.

° After a total of 4 hours of exposure; once the device is turned off after 20 minutes of use, it is assumed that the person remains in the room for 3 hours and 40 minutes.

The MOEs to violet oil from food (based on its potential use as a flavouring agent), eye moisturizer, leave-on hair conditioner, facial cleanser, body moisturizer, massage oil (9 years and above), lipstick, and body fragrance are considered adequate to address uncertainties in the health effects and exposure data used to characterize risk.

In addition, the use of violet oil in a massage oil (8 years and younger) are below 300, which accounts for uncertainties with respect to interspecies extrapolation, intraspecies extrapolation, the POD, and the adequacy of the database and is considered potentially inadequate.

The use of violet oil as a DIY bath oil product and a DIY body moisturizer is considered adequate to address uncertainties in the health effects and exposure data used to characterize risk.

The MOEs between the critical effect level and the estimates of daily exposure from the use of violet oil in DIY aromatic diffuser, as a DIY facial steamer (during the use of the device), and once the device is turned off after 20 minutes of use are below 300, which account for uncertainties with respect to interspecies extrapolation, intraspecies extrapolation, the POD, and the adequacy of the database and are considered potentially inadequate.

7.1.4 Uncertainties in evaluation of risk to human health

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

Table 7-23. Sources of uncertainty in the risk characterization for violet oil

Key source of uncertainty	Impact
Limited hazard data are available for violet oil and its main component, 2,6-nonadienal. The read-across analogue, 2,4-hexadienal, was used to inform the risk assessment.	+/-
There are no suitable dermal or inhalation toxicity studies available for 2,4-hexadienal; therefore, route-to-route extrapolation for violet oil was carried out for inhalation exposure scenarios using a critical effect level from an oral study, and a dermal POD was not determined.	+/-

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

7.5 Aldehyde subgroup 2 (lilial, verdantiol, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, vernaldehyde)

7.5.1 Exposure assessment

Environmental media

Considering the low quantity (<100 kg) of the substance submitted in response to a CEPA section 71 survey (Environment Canada 2013), exposure to verdantiol, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, and vernaldehyde from environmental media is not expected.

In 2011, the National Research Council of Canada (NRC) examined the presence of 954 organic chemicals from four databases on building materials, indoor air, and dust samples. A subset of data from a 2010 NRC study involving indoor air and dust samples from 115 homes in Quebec City was analyzed to identify certain chemicals, including lilial. The maximum reported concentrations were 28.99 µg of lilial/g of dust and 3.76 µg/m³ in indoor air (NRC 2011). Lilial was also quantified in indoor air by examining the gas chromatographs of indoor air samples collected in two field monitoring studies measuring volatile organic compounds in indoor air at 36 homes in Ottawa in 2014 (that is, the garage study) and 54 homes in Nunavik in 2018 (that is, Nunavik study). Lilial was not detected at levels above the method detection limit (that is, 2 ng) in Ottawa, but it was detected in 9% of samples collected in Nunavik. The air concentrations of lilial from samples above the method detection limit ranged from 0.4 µg/m³ to 0.7 µg/m³ (n=5) (NRC 2019). As the air concentrations in indoor air were higher in the Quebec City study, this study was used to calculate potential exposure to lilial from indoor air.

Measured concentrations of lilial in ambient air, water, or soil were not identified in Canada. The level III fugacity model known as ChemCAN (2003) was used to derive predicted environmental concentrations using the quantities reported in Canadian commerce for 2011 for lilial (Environment Canada 2013), that is, 25 370.22 kg (manufacturing and imports). The estimated concentrations in air, water, and soil were 5.50 x 10⁻⁵ µg/m³, 3.34 x 10⁻³ µg/L, and 0.32 ng/g, respectively.

Exposure to lilial from environmental media was estimated using the predicted concentrations in ambient air, water, and soil, and the maximum concentrations of lilial measured in indoor air and dust in the Quebec City study (NRC 2011). Estimated exposure ranged from 6.70 x 10⁻⁴ mg/kg bw/day to 2.49 x 10⁻³ mg/kg bw/day for adults to 1-year-olds, respectively.

Products available to consumers

Lilial is present in products available to consumers. To evaluate the potential for exposure to lilial from cosmetics and NHPs applied by the dermal route, sentinel scenarios were selected based on a combination of use frequencies and reported concentrations of lilial in these products. The selected sentinel scenarios represented the highest exposures, relative to other dermally applied cosmetics, and NHPs based on identified products reported to contain these substances. Exposure to lilial from the use of body fragrance; liquid body cleanser; wash-off hair conditioner; massage oil; body moisturizer; face makeup; nail polish; nail polish remover; depilator; antiperspirant/deodorant; bath product; facial moisturizer; acne treatment (NHP); antiseptic skin cleanser (NHP); hair colour; hair straightening, waving, and curling product; and sunless tanning product for the face (non-SPF) were considered to be the

sentinel scenarios for dermal application (personal communication, email from the Consumer and Hazardous Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2020; unreferenced; personal communication, email from the Natural and Non-prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, 2021; unreferenced).

Given the widespread use of lilial in products available to consumers, it was selected as a chemical of relevance for human biomonitoring (HBM) in Germany. In the first HBM study on lilial, 2133 children and adolescents (both sexes) aged 3 to 17 years provided void urine samples that were analyzed (Murawski et al. 2020). Four main metabolites, that is, tert-butylbenzoic acid (TBBA), lysmerol, lysmerylic acid, and hydroxy-lysmerylic acid, were found in quantifiable amounts with maximum concentrations of 315, 91.1, 8.97 and 39.7 µg/L, respectively; mean concentrations of 10.21 µg/L for TBBA, 1.528 µg/L for lysmerol, and concentrations below the limit of quantification of 0.2 µg/L and 0.4 µg/L for lysmerylic acid and hydroxy-lysmerylic acid, respectively, were also found (Murawski et al. 2020). In addition, the same metabolites were measured in urine samples from 329 young adults aged 20 to 29 years. These samples were provided by the German Environment Agency to investigate exposure to lilial between 2000 and 2018 (Scherer et al. 2021). The maximum concentrations were 84.72, 14.02, 31.32, and 29.23 µg/24-hour, and mean concentrations were 13.73, 1.78, 0.99, and 3.41 µg/24-hour for TBBA, lysmerol, lysmerylic acid, and hydroxy-lysmerylic acid, respectively. A significant decline of these metabolites was observed over the sampling years (Scherer et al. 2021).

Lilial has been identified in a carpet deodorizer product (SDS 2017a). Lilial has also been identified in various air freshener products (solid gel, liquid plug-in, and air spray) (SDS 2016, 2017a, 2019) at concentration ranges from 0.1% to 5%. Exposure was quantified from a solid gel air freshener product (SDS 2016) and a liquid plug-in (SDS 2017a).

Following occlusive dermal application of lilial (6.8 mg/kg bw/day in 70% ethanol on the back skin of rats), a mean cumulative total of 14.6% of the dose was excreted in urine, 0.8% was recovered in cage washings, and 2.0% was excreted via feces (levels in expired air traps were not detectable). The remaining radioactivity in all tissues investigated was 1.2% of the initial dose (site of application). The mean total proportion of the applied dose was ~19% in excreta and tissues up to 120 hours after application (SCCS 2016; RIFM 2020).

To estimate systemic exposure for the aldehydes subgroup 2 substances, estimated oral, inhalation, and dermal exposures were summed, where appropriate. A dermal absorption factor of 15%, based on a chemical-specific human *in vitro* study for lilial, was used (SCCS 2019). The estimated dermal absorption value was a high-end estimate from four different formulation groups with observed dermal absorption values ranging from 8.5% to 13.5% (including skin-bound residues and the addition of two standard deviations for two groups and one standard deviation for the other two dose

groups). To account for the amount of product absorbed by the dermal route, the product amount available for inhalation was adjusted by 85%, except in the case of body moisturizer. For body moisturizer, since the product amount for inhalation was adjusted for the exposed surface area, and this value was less than 85% of the product amount, no further adjustment was made to the product amount.

Estimates of systemic exposures to lilial for the lowest and highest exposed age groups are summarized in Table 7-24.

Table 7-24. Daily estimated exposures from products available to consumers for lilial

Product scenario	% in product	Route(s) of exposure	Exposure range (mg/kg bw/day) ^a
Body fragrance	44%	Dermal and inhalation	0.54 (adults) to 1.52 (2–3 years)
Liquid body cleanser	1%	Dermal and inhalation	3.24×10^{-3} (adults) to 1.3×10^{-2} (0–5 months)
Hair conditioner (wash-off)	2%	Dermal and inhalation	5.06×10^{-3} (14–18 years) to 1.06×10^{-2} (2–3 years)
Massage oil	0.3%	Dermal and inhalation	2.58×10^{-2} (adults) to 1.38×10^{-1} (0–5 months)
Body moisturizer	1%	Dermal and inhalation	2.17×10^{-1} (adults) to 4.84×10^{-1} (0–5 months)
Face makeup liquid	1%	Dermal and inhalation	1.30×10^{-2} (14–18 years) to 2.69×10^{-2} (4–8 years)
Nail polish	3%	Dermal and inhalation	9.73×10^{-3} (adults) to 1.80×10^{-2} (2–3 years)
Nail polish remover	0.1%	Dermal and inhalation	5.86×10^{-2} (adults) to 1×10^{-2} (9–13 years)
Hair removal/depilator	0.1%	Dermal and inhalation	3.67×10^{-3} (14–18 years) to 4.46×10^{-3} (adults)

Product scenario	% in product	Route(s) of exposure	Exposure range (mg/kg bw/day)^a
Antiperspirant/deodorant (solid)	3%	Dermal and inhalation	5.18×10^{-2} (9–13 years) to 8.63×10^{-2} (14–18 years)
Antiperspirant/deodorant (spray)	0.3%	Dermal and inhalation	1.01×10^{-2} (9–13 years) to 2.67×10^{-2} (14–18 years)
Bath product	3%	Dermal and inhalation	9.18×10^{-4} (9–13 years) to 2.83×10^{-3} (14–18 years)
Facial moisturizer	3%	Dermal and inhalation	1.32×10^{-1} (14–18 years) to 2.11×10^{-1} (adults)
Permanent hair colour	1%	Dermal and inhalation	2.69×10^{-1} (adults) to 3.21×10^{-1} (14–18 years)
Temporary hair colour	0.11%	Dermal and inhalation	8.33×10^{-3} (adults) to 2.59×10^{-2} (4–8 years)
Hair straightening, waving, and curling product	11%	Dermal and inhalation	1.62×10^{-1} (adults) to 4.31×10^{-1} (4–8 years)
Sunless tanning product for the face (lotion)	1%	Dermal and inhalation	3.35×10^{-2} (adults) to 3.94×10^{-2} (14–18 years)
Acne treatment (NHP)	0.1%	Dermal and inhalation	2.23×10^{-4} (adults) to 3.53×10^{-4} (9–13 years)
Antiseptic skin cleanser (NHP)	0.007%	Dermal and inhalation	3.56×10^{-4} (14–18 years) to 1.05×10^{-3} (2–3 years)
Antiseptic skin cleanser (NHP) ^b	0.007%	Dermal and inhalation	5.33×10^{-3} (adults) to 2.63×10^{-2} (2–3 years)
Carpet deodorizer (application)	1%	Dermal and inhalation	7.71×10^{-4} (adults)
Post-application exposure to cleaned carpets	1%	Dermal, inhalation, and incidental oral	1.31×10^{-2} (1 year old)

Product scenario	% in product	Route(s) of exposure	Exposure range (mg/kg bw/day) ^a
Solid gel air freshener	5%	Inhalation	5.31 x 10 ⁻² (adults) to 2.11 x 10 ⁻¹ (1 year)
Liquid plug-in air freshener	3%	Inhalation	1.37 x 10 ⁻² (adults) to 4.87 x 10 ⁻² (1 year)

^a Only lowest to highest exposed age groups are presented. Calculation details are in Appendix A.

^b For situations of public health concern, the use of hand sanitizers among the general population may increase up to 25 uses per day (personal use by adults, increased use by children in schools and child care facilities) (RIVM 2021a)

No Canadian uses in products available to consumers, food packaging materials, or incidental additives have been identified for myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, vernaldehyde, and verdantiol.

An industry submission indicated that lilial, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde may be present as fragrance ingredients in products available to consumers, and these products are present in the following categories: leave-on cosmetics (that is, less than 0.05%), rinse-off cosmetics (that is, less than 0.1%), air fresheners (that is, less than 2.5%), and cleaning products (that is, less than 0.05%). In order to evaluate the potential exposure of the general population to these substances from the use of these categories of products, representative sentinel exposure scenarios were selected. These scenarios describe the highest level of exposure to these substances from product use, taking into consideration frequency of use and concentrations. Therefore, a body moisturizer at 0.05%, a body cleanser at 0.1%, a liquid air freshener at 2.5%, and a liquid laundry detergent machine at 0.05% represent the sentinel scenarios for the leave-on cosmetics, rinse-off cosmetics, air fresheners, and cleaning products categories, respectively. Estimates of systemic exposures for the lowest and highest exposed age groups are summarized in Table 7-25.

Table 7-25. Daily estimated exposures from products available to consumers for lilial, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde

Product scenario	% in product	Route(s) of exposure	Exposure range (mg/kg bw/day) ^a
Leave-on cosmetics	0.05%	Dermal and inhalation	1.08 x 10 ⁻¹ (adults) to 2.42 x 10 ⁻² (0–5 months)
Rinse-off cosmetics	0.1%	Dermal and inhalation	1.71 x 10 ⁻³ (adults) to 4.37 x 10 ⁻³ (0–5 months)

Product scenario	% in product	Route(s) of exposure	Exposure range (mg/kg bw/day) ^a
Air fresheners	2.5%	Inhalation	1.14 x 10 ⁻³ (adults) to 4.07 x 10 ⁻³ (1 year)
Cleaning products	0.05%	Dermal and inhalation	1.66 x 10 ⁻⁵ (14–18 years) to 5.6 x 10 ⁻⁴ (adults)

^a Only lowest to highest exposed age groups are presented. Calculation details are in Appendix A.

7.5.2 Health effects assessment

There are seven discrete substances in aldehydes subgroup 2 (lilial, verdantiol, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde).

There is no hazard information available for verdantiol, myrmac-aldehyde, and myrmac-carboxaldehyde. For myrac-aldehyde and vernaldehyde, there is limited hazard information available consisting of skin sensitization data. Cetonal was evaluated by the NICNAS on the basis of limited available hazard information on skin sensitization and genotoxicity (NICNAS 2016b).

Myrac-aldehyde is not considered to be a skin sensitizer based on the findings from a maximization test in which 23 human volunteers did not have a sensitization reaction following exposure to 3% myrac-aldehyde in petrolatum (Fragrance raw materials monographs 1976).

Vernaldehyde is not considered to be a skin sensitizer based on the findings from a repeated-insult patch test in which human volunteers (n=52) did not have a sensitization reaction following exposure to 2% vernaldehyde in dimethyl phthalate (Ford et al. 1992).

Cetonal is considered to be a skin sensitizer in female mice based on the positive results seen in a local lymph node assay conducted according to OECD Test Guideline 429 (NICNAS 2016b). Cetonal was considered a non-sensitizer in the KeratinoSen assay since the luciferase gene was induced at cytotoxic concentrations (ECHA Registration dossier 2020d).

Cetonal showed negative results in an *in vitro* point mutation assay (Ames test) in *S. typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537, with or without metabolic activation (NICNAS 2016b; ECHA Registration dossier 2020d).

In the absence of hazard data on these substances, a read-across approach was taken, and hazard information on the analogue, lilial, was used to inform the health effects assessment.

Lilial is a synthetic substance that has not been reported to occur in nature (Arnau et al. 2000), whereas the other five substances in aldehydes subgroup 2 are naturally

occurring and belong to the class of terpenes. Lilial is a racemic mixture covering two enantiomers, namely (2S)-3-(4-tert-butylphenyl)-2-methylpropanal and (2R)-3-(4-tert-butylphenyl)-2-methylpropanal (SCCS 2019). The seven substances within aldehydes subgroup 2 are all aromatic aldehydes, characterized by a six carbon ring and possessing multiple methyl groups and a carbonyl group on the side chain. However, lilial possesses three double bonds in the ring structure (benzene ring), whereas the other aldehydes in aldehydes subgroup 2 only have one. In addition, the position of the carbonyl group differs for each substance. For example, the carbonyl group is present on the side chain farther away from the ring for lilial and cetonal, whereas for the other substances, it is found closer to the ring structure. Finally, myrac-aldehyde and myrmac-aldehyde both possess one double bond in the side chain, unlike the other substances in the subgroup that do not have double bonds (except for the carbonyl group). Human and animal studies show clear evidence of systemic absorption of lilial via the oral and dermal routes as well as high bioavailability via the oral route (SCCS 2016). There are no toxicokinetics data on the analogues, but they are also likely to have high bioavailability via the oral route as their physical and chemical properties are very similar to those of lilial. Target and analogues are simple aldehydes, and therefore, all have structural alerts for genotoxicity as well as *in vitro* and *in vivo* mutagenicity on QSAR Toolbox, version 4.2 (OECD 2016).

Verdantiol is a Schiff base substance synthetically prepared from an aldehyde (lilial) and an amine (methyl anthranilate). The preparation of Schiff bases is a reversible reaction, which means that verdantiol is unstable and prone to hydrolysis to regenerate the original aldehyde, lilial. The stoichiometric presence of lilial of the verdantiol is taken into account, assuming 100% dissociation as default based on the absence of data on verdantiol.

An amendment to the *CLP Regulation* was made on August 2020 to classify lilial as Reproductive toxicant category 1B (presumed human reproductive toxicant based on animal studies) based on evidence of reproductive toxicity, and lilial has been prohibited in cosmetics in Europe since March 2022. Lilial is also under assessment by ECHA as a potential endocrine disruptor. Furthermore, lilial is classified as a reproductive toxicant according to the harmonized classification and labelling approved by the EU and is included on their candidate list for authorization as a substance of very high concern.

Toxicokinetics

After semi-occlusive dermal application of ¹⁴C-lilial (11.37 mg of lilial in 70% ethanol on 10 cm² of back skin) on three human volunteers for 6 hours, a mean of 1.4% of the applied dose was excreted in urine within 24 hours, and radioactivity was below the detection limit in urine samples of later time points and in all feces and blood plasma samples (SCCS 2016).

Based on multiple lines of evidence (Hunter et al. 1965; Cagen et al. 1989), the toxicity of lilial on the male reproductive tract in rats is hypothesized to be due to the formation of the metabolite p-tert-butyl-benzoic acid (TBBA), more specifically the TBBA

coenzyme A (CoA) conjugate formed (McCune et al. 1982). Lilial and the metabolite TBBA is rapidly transformed to TBBA-CoA in rat hepatocytes, leading to an accumulation of stable levels of this conjugate, which was not detectable in human hepatocytes; this indicates a species-specific effect in the mechanism of toxicity of lilial where rats seem to be more sensitive than humans (Laue et al. 2017).

The possible estrogenic activity of lilial was investigated in an assay in MCF7 human breast cancer cells *in vitro* (Charles et al. 2009). Lilial partially displaced [³H]-estradiol from recombinant human estrogen receptors ER α and ER β and from cytosolic estrogen receptor of MCF7 cells (Charles et al. 2009). Furthermore, lilial increased the expression of a stable integrated estrogen-responsive reporter gene and of the endogenous estrogen-responsive pS2 gene in MCF7 cells (Charles et al. 2009). On the basis of these observations, the authors concluded that lilial can induce estrogenic responses in the MCF7 human breast cancer cell line *in vitro*. However, no studies are available on the potential estrogenic activity of lilial *in vivo*.

Repeated-dose toxicity studies

In a study compliant with OECD Test Guideline 408, lilial was orally administered to female and male Albino rats (14/sex/dose) by gavage at doses of 0, 2, 5, 25, or 50 mg/kg bw/day, 5 days a week for 13 weeks (SCCS 2016; ECHA Registration dossier 2020e). The animals in the control and the high-dose groups had a post-treatment recovery of four weeks. At ≥ 25 mg/kg bw/day, dose-dependent increases in absolute and relative liver and adrenal weights were observed in both sexes, but these changes were reversible in the recovery (high-dose) group. Furthermore, a significant decrease in plasma cholinesterase activity (30% and 70% compared to controls) and lower plasma cholesterol levels were observed at 25 and 50 mg/kg bw/day in both sexes, but these changes were also reversible in the recovery group. There was an increased incidence of testicular atrophy and spermatoceles in the epididymis in males at 50 mg/kg bw/day. Disturbances of spermatogenesis and spermiogenesis, testicular increases in Sertoli cell-only tubules, and increased surface density in Leydig cells were described, along with a decreased density of spermatozoa, nucleated cells, and spermatoceles in the epididymis at 50 mg/kg bw/day. In the four-week recovery group, the effects on the male reproductive organs persisted after treatment. A NOAEL of 25 mg/kg bw/day for testicular toxicity was determined by the study authors (SCCS 2016; ECHA Registration dossier 2020e).

In a subchronic toxicity study, beagle dogs (3/sex/dose) were orally administered daily capsules containing 0, 4.4, 22.3, or 44.6 mg/kg bw/day lilial, 7 days a week for 13 weeks (SCCS 2016). No mortality occurred, and no significant differences in body weight gains were observed. No treatment-related effects were reported for clinical signs and chemistry. Gross pathology and histopathology revealed no specific substance-related findings; in particular, there were no alterations on reproductive organs in males or females (SCCS 2016). In a subsequent study by the same authors, in which three female beagle dogs were orally administered 200 mg/kg bw/day lilial in

the form of capsules for 13 weeks, similarly to the previous study, no treatment-related effects were found (SCCS 2016; CLH 2017).

In an explorative dose-escalation study, two male dogs were treated with lilial at increasing doses of 50 µL/kg bw/day from days 1 to 7; 100 µL/kg bw/day from days 8 to 14; 200 µL/kg bw/day from days 15 to 21; 400 µL/kg bw/day from days 22 to 50; and 600 µL/kg bw/day from days 51 to 64 (corresponding to 47 mg/kg bw/day up to 564 mg/kg bw/day) (SCCS 2016; CLH 2017). This study indicated occasional vomiting in both animals, diarrhea in one animal, and body weight reduction together with an increase in glutamate dehydrogenase and alanine aminotransferase levels. Histological examinations showed multifocal inflammation in the liver and mild atrophy in seminiferous tubules in both animals (necrosis of germ cells, multinucleated giant cells in tubular lumen) (SCCS 2016; CLH 2017).

In a one-generation reproductive toxicity range-finding study, male and female Wistar rats (10/sex/dose) were orally administered 0, 400, 800, 1700, or 3400 ppm (equivalent to 14.5, 28.7, 62.6, or 119.7 mg/kg bw/day, respectively) of lilial microencapsulated in the feed during the pre-mating (six weeks) and mating periods for both sexes and throughout gestation and lactation (14 weeks) for F0 dams only (SCCS 2016; NICNAS 2016c; CLH 2017). F0 males showed a dose-dependent decrease in body weights and body weight gains, along with a reduction in food consumption in the 3400 ppm group. Increases in relative liver weights starting at 800 ppm and decreases in relative kidney weights in the 3400 ppm group were observed in F0 males only. In F0 males, increased levels of plasma alanine aminotransferase, alkaline phosphatase, and glutamate dehydrogenase were observed at 1700 and 3400 ppm, and increased levels of plasma gamma-glutamyltransferase were observed only at 3400 ppm. Effects on male reproductive organs were observed at 1700 and 3400 ppm, including decreases in relative testes and cauda epididymis weights, diffuse testes degeneration, and aspermia of the epididymis. In the 3400 ppm male group, a decrease in seminal vesicle and prostate weights was observed as well as hyperplasia of Leydig cells. F0 dams showed decreases in body weights and body weight gains in the 800 ppm group and at higher doses during and after pre-mating. During gestation and lactation, mean maternal body weights and body weight gain were decreased in the 800 ppm group, and food consumption was decreased during lactation compared to controls. A 2-8 fold increase in serum levels of gamma-glutamyltransferase and a decrease of between 50% and 65% in serum cholinesterase levels compared to controls were seen in all dose groups in F0 dams. No viable offspring was produced from animals in the 1700 and 3400 ppm groups. At 1700 ppm, only one of eight mated females became pregnant, and only had one implantation, which was finally resorbed (post-implantation loss). In the 400 and 800 ppm groups, non-significant increases in mean implantation losses and decreases in the mean number of delivered pups per dam were observed. Post-natal survival was non-significantly decreased between days 0 and 4 in the 400 and 800 ppm groups, and no pup mortality was observed between PNDs 4 and 21. Pup weight at birth and weaning and pup body weight gain were also reduced in the 400 and 800 ppm groups. Based on these results, the authors suggested the dose of 400 ppm (~14.5 mg/kg bw/day) as a NOAEL in males and a LOAEL in dams for systemic toxicity and

determined a NOAEL of 800 ppm (~28.7 mg/kg bw/day) for male reproductive toxicity (SCCS 2016; NICNAS 2016c; CLH 2017).

In a developmental toxicity study compliant with OECD Test Guideline 414, pregnant rats (25/dose) were orally administered 0, 5, 15, or 45 mg/kg bw/day (effective doses: 0, 4.1, 12.7, or 40.7 mg/kg bw/day, respectively) lilial by gavage in olive oil from GDs 6 to 20 (SCCS 2016; NICNAS 2016c; CLH 2017). No mortality occurred, but signs of maternal toxicity were observed at 15 and 45 mg/kg bw/day. Increases in mean alanine aminotransferase levels (20% to 30% above control) and decreases in serum cholinesterase levels (20% to 45% below control) were found in the 15 and 45 mg/kg bw/day groups, and mean glutamate dehydrogenase levels were increased (79% above controls) in the 45 mg/kg bw/day dose group. Increases in absolute and relative liver weights were found at all dose levels, with histopathological findings at 15 and 45 mg/kg bw/day, and uterus weights were reduced (20% below controls) at 45 mg/kg bw/day, though not significantly. Mean food consumption was reduced (18% below controls) in the high-dose group on days 6 to 8 post coitum (p.c.) but was comparable to controls by study termination. Although no decrease in food consumption was observed in mid-dose animals, mean maternal weight gains decreased on days 6 to 8 p.c. (56% below controls) but recovered during the study period. At 45 mg/kg bw/day, maternal mean body weight loss was observed on days 6 to 8 p.c., and the mean body weight gain was reduced (25% below controls) over the entire treatment phase. Mean post-implantation losses were increased in the high-dose group: resorptions were observed at 15.1% per dam compared to 4.4%, 4.7%, and 4.9% at 0, 5 and 15 mg/kg bw/day, respectively. Signs of prenatal developmental toxicity were observed at 15 and 45 mg/kg bw/day, consisting of reduced mean fetal body weights and an increase in mean percentages of skeletal variations per litter (delays and disturbances in ossification of the skull, sternebra, and pubic girdle). Malformations were observed in 3 out of 170 high-dose group fetuses (1.8% of all high-dose group fetuses; 3 out of 23 litters affected), including anasarca, polydactyly, and cervical hemivertebra. A NOAEL of 4.1 mg/kg bw/day was determined by the authors for maternal and prenatal developmental toxicity at higher doses (SCCS 2016; NICNAS 2016c; CLH 2017).

In a modified extended one-generation reproduction toxicity study following OECD Test Guideline 443, encapsulated lilial was administered to male and female Wistar rats (35-40/sex/dose) at nominal doses of 0, 1, 3, or 10 mg/kg bw/day (equivalent to 0, 1.4, 4.5, or 15.1 mg/kg bw/day, respectively) in food (CLH 2017; SCCS 2019; RIFM 2020). F0 animals were treated with lilial for approximately two weeks prior to mating, through mating (up to two weeks), and for a maximum of six post-mating weeks (males) or gestation (three weeks) and lactation (three weeks) for females. Pups of the F1 litter were assigned to seven different cohorts (cohorts 1A, 1B, 2A, 2B, 3, 4A, and 4B) for assessment of specific (histo-) pathological examinations and were maintained on the test diet until sacrifice. Cohort 1B was selected to produce F2 pups. Cohorts 1 (A/B) were examined for reproductive toxicity, cohorts 2 (A/B) for developmental neurotoxicity, cohort 3 for developmental immunotoxicity (DIT), and cohorts 4 (A/B) for acetyl cholinesterase activities in F0 animals, PND 4 surplus pups, and PND 22 and adolescent F1 offspring. The study was terminated with the sacrifice of the F2

weanlings and F1 cohort 1B parental animals. There were no test substance-related mortalities reported. Maternal body weights were significantly reduced compared to controls in the high-dose F0 and F1 females during gestation and lactation. Absolute ovary weights (100, 99, 94, and 88 mg at 0, 1, 3, and 10 mg/kg bw/day, respectively) and relative ovary weights (100, 96, 93, and 89 mg at 0, 1, 3, and 10 mg/kg bw/day, respectively) were reduced in a dose-dependent manner in the F0 females, reaching statistical significance at the high dose. Some changes in blood and enzyme parameters were observed at 10 mg/kg bw/day, such as a prolonged prothrombin time in F0 and F1 for both sexes and increased γ -glutamyl transferase activity and reduced albumin levels in F0 and F1 females. At 10 mg/kg bw/day, higher red blood cell counts and hemoglobin values were detected in F0 females and F1 males and females. Higher hematocrit levels were also noted in F0 females at this dose. A decrease in mean serum acetylcholinesterase activities was seen in F0 females (16% in mid-dose and 21% in high-dose animals below controls) and other peripheral tissues including erythrocytes. In the F0 high-dose males, a decrease in the mean acetylcholinesterase activities of the musculus gastrocnemius (18% below controls) was observed. In the high-dose F0 females and F1 females (cohorts 1A and 1B), an increase in absolute and relative liver weights (119% and 120% above controls, respectively) was observed, associated with minimal to slight centrilobular hypertrophy and accompanied by minimal to slight apoptosis/single cell necrosis of hepatocytes. The only notable findings on reproductive parameters were slightly and non-significantly higher mean percentages of abnormal sperms (3.5% above control) in the cauda epididymis in the high-dose F0 males. Pup body weight of the high-dose F1 and F2 offspring was 14% to 16% lower than controls after birth and did not recover until weaning. In high-dose F1 females, a decrease in the mean number of implantation sites as well as a decrease in the mean number of F2 pups delivered were observed. Lower peripheral acetylcholinesterase activities in serum erythrocytes and diaphragm tissue were found in male F1 pups at PND 4 and in females at PND 76 of the high-dose group (up to 50% of the means in control animals). No corresponding clinical signs of developmental neurotoxicity were evident in male and female F1 offspring at any dose level. There were no treatment-related effects on motor activity, auditory startle habituation, or in the field observation battery following exposure to the test compound in these animals. The only notable findings in neurobehavioural testing were lower maximum amplitudes in the auditory startle response test for the high-dose F1 males only, and no corresponding effects were recorded for startle response latency. Regarding neuropathology, brain weight determination, brain length and width measurements, and brain morphometry and neuropathological examination by light microscopy did not reveal any neurotoxicological treatment-related findings. Neither T-cell dependent anti-SRBC IgM antibody response, nor absolute and relative lymphocyte cell counts in the spleen tissue showed any treatment-related changes, indicating no evidence of any DIT induced by lillial. On the basis of these results, the authors determined a NOAEL for systemic toxicity of 3 mg/kg bw/day (effective dose: 4.5 mg/kg bw/day) for the F0 and F1 parental animals as well as the adolescent animals; a NOAEL for developmental toxicity of 3 mg/kg bw/day (effective dose: 4.5 mg/kg bw/day) in the F1 and F2 progeny; and a NOAEL for reproductive performance of 10 mg/kg bw/day (effective dose: 15.1 mg/kg bw/day), the

highest dose tested, in the F0 and F1 parental rats (CLH 2017; SCCS 2019; RIFM 2020).

In the only dermal toxicity study, undiluted lilial was applied as occlusive patches on the back of albino rats (5 males/group) for six hours, at doses of 0, 250, 500, 1000, or 2000 mg/kg bw/day for five consecutive days (SCCS 2016; NICNAS 2016c; CLH 2017). A slight decrease in body weight and marked testicular atrophy were noted at 2000 mg/kg bw/day. Seminiferous tubules with disorganization of the epithelial structure, decreases in the number of germ cells, and increases in the number of degenerating germ cells (including giant cells) were observed in combination with immature/degenerating germ cells in epididymis and the presence of spermatoceles at 2000 mg/kg bw/day. No further observations were performed to assess adverse effects other than testicular toxicity. The study authors considered the NOAEL to be 1000 mg/kg bw/day based on the effects observed on the reproductive organs at the highest dose tested (NICNAS 2016c; SCCS 2016; CLH 2017).

Rats and mice (5 males/group) were administered 50 mg/kg bw/day lilial and lysmerylic acid (metabolite of lilial) in olive oil by gavage for 1, 2, 3, 4, or 14 days, with the main focus on reproductive organ toxicity (SCCS 2016; CLH 2017). No mortality occurred, and no clinical signs were reported for both rats and mice. In rats, slight to severe testicular atrophy, with an incidence of 2/5 animals after a single application of lilial and in all animals after longer application periods, was observed. In mice, a reduction in the ratio of normal to abnormal sperm was observed after exposure to lilial for three and four days only, but no histopathological changes in the testes were noted. However, longer treatment periods did not influence this parameter or other sperm parameters, such as sperm motility and spermatid count in testes or cauda epididymis (SCCS 2016; CLH 2017).

Several explorative oral gavage studies conducted for five consecutive days in rats at doses ranging from 25 mg/kg bw/day to 400 mg/kg bw/day showed clinical signs of toxicity, body weight loss, and macroscopic changes in the liver starting from 50 mg/kg bw/day (SCCS 2016; NICNAS 2016c; CLH 2017). At the same dose level, degeneration and loss of germ cells in the seminiferous epithelium were found. However, decreased testes and kidney weights and decreased sizes of prostate and seminal vesicles became evident at higher dose levels, which were not specified in the study (SCCS 2016; NICNAS 2016c; CLH 2017).

Five male mice and five male guinea pigs administered a daily oral dose of 100 mg/kg bw/day of lilial for five consecutive days showed no signs of systemic toxicity, including testicular toxicity (SCCS 2016; NICNAS 2016c; CLH 2017).

Five male rabbits treated for 15 days via gavage with lilial at 30, 100, or 300 mg/kg bw/day showed no treatment-related findings on clinical observations, body weight, and food consumption (SCCS 2016; NICNAS 2016c; CLH 2017). At 30 mg/kg bw/day, one animal showed a moderate degeneration of the seminiferous tubules, and moderate oligospermia and moderate inflammation in the epididymis. At 100 mg/kg bw/day,

reduced testes and epididymides sizes with severe diffuse degeneration of seminiferous tubules and severe atrophy plus aspermia in the left epididymis were observed. However, sperm evaluation did not reveal any treatment-related effect in this or any other treated animal, and a dose-response relationship could not be observed. These effects were not considered to be treatment-related by the study authors (SCCS 2016; NICNAS 2016c; CLH 2017).

Beagle dogs (4 males/group) were administered oral doses of lilial via gelatine capsules at 0, 40, 200, or 1000 mg/kg bw/day for two weeks (SCCS 2016; NICNAS 2016c; CLH 2017). Due to occurrences of vomitus and diarrhea at 1000 mg/kg bw/day, the high dose was lowered to 500 mg/kg bw/day starting on day 3. At the mid- and high-dose groups, increased liver weight and centrilobular hypertrophy of hepatocytes was observed. At 200 mg/kg bw/day, one dog showed degeneration of seminiferous tubules, hyperplasia of Leydig cells, and aspermia and epithelial vacuolation in the epididymis (SCCS 2016; NICNAS 2016c; CLH 2017). A follow-up study in 10 male dogs administered 200 mg/kg bw/day of lilial for two weeks led to severe body weight loss, anemia, increased liver weight, and decreased prostate and testes weight with histomorphological correlates. Altered sperm quality and reduced sperm motility were also noted (SCCS 2016; NICNAS 2016c; CLH 2017).

Two male Rhesus monkeys were orally administered lilial in food at 0 or 100 mg/kg bw/day for five days (SCCS 2016; NICNAS 2016c; CLH 2017). Only small foci in one epididymis of one animal and small hollow spaces in the epithelium of one epididymis of the other animal were observed. The testes of both animals were found to be free of lesions. According to the study authors, the findings in one epididymis of each animal do not represent a test substance-related effect since other male reproductive tissues were not affected (SCCS 2016; NICNAS 2016c; CLH 2017).

The toxicity studies on lilial show adverse reproductive effects in most animal species tested (rats, mice, dogs, rabbits, and monkeys), with the rat being the most sensitive and showing adverse effects on the male reproductive organs at lower doses compared with the other species.

Genotoxicity

Lilial showed negative results in an Ames test using *S. typhimurium* strains TA1535, TA1537, TA1538, TA97, TA98, TA100, and TA102, with or without metabolic activation (Di Sotto et al. 2014; SCCS 2016; NICNAS 2016c). Similarly, another bacterial reverse mutation assay on *S. typhimurium* strains TA98, TA100, and TA1537 and *E. coli* strain WP2 uvrA gave negative results in the presence and absence of S9-mix (SCCS 2019). However, increased numbers of revertants in the absence of S9-mix were observed in this reverse mutation assay for the *S. typhimurium* strain TA1535 in the plate incorporation test (but not in the follow-up pre-incubation test), although the authors considered lilial to be non-mutagenic in this assay since the increases observed were not reproducible, were associated with cytotoxicity, and did not show a dose trend (SCCS 2019). A mammalian cell gene mutation assay using Chinese hamster lung

fibroblasts (V79) showed significant increases in mutant frequency. However, the authors concluded that lilial was not mutagenic under the study conditions since the increases observed were not dose-dependent or reproducible (ECHA Registration dossier 2020e; SCCS 2016; NICNAS 2016c). Lilial did not induce any significant increases in the mutant frequency at the TK +/- locus in L5178Y cells in another gene mutation test using a mouse lymphoma assay (ECHA Registration dossier 2020e). Lilial did not induce single-strand DNA breaks in an alkaline Comet assay in human colonic epithelial cells (Di Sotto et al. 2014). In a non-guideline micronucleus assay on human lymphocytes, lilial showed no increase in the micronuclei frequency in comparison with the control (Di Sotto et al. 2014). In contrast, lilial induced numerical and structural chromosomal aberrations in the absence of S9-mix and a concentration-dependent increase of structural aberrations in the presence of S9-mix in a mammalian chromosome aberration test using Chinese hamster ovary cells (SCCS 2016; NICNAS 2016c).

In an *in vivo* micronucleus study, lilial was injected intraperitoneally into mice (5/sex/dose) at a dose of 150, 300, or 600 mg/kg bw/day. An increase in the sum of micronucleated polychromatic erythrocytes in the high-dose group was observed only in males 48 (but not 24) hours post treatment. However, the study authors concluded that lilial showed no clastogenic potential as the increases observed were within the historical controls range, were not dose-dependent, and were not observed in any other dose group (ECHA Registration dossier 2020e; SCCS 2016; NICNAS 2016c).

7.5.3 Characterization of risk to human health

The critical effect level identified for the aldehydes subgroup 2 is an oral NOAEL of 4.1 mg/kg bw/day from a developmental toxicity study in rats exposed to lilial and based on adverse effects in the dams and fetuses at higher doses. This effect level is based on pathological changes in the liver and decreases in acetylcholinesterase levels in dams at 12.7 mg/kg bw/day, decreased fetal body weights and increased incidence of skeletal variations in fetuses at 12.7 mg/kg bw/day, and decreases in maternal body weight and increases in post-implantation losses at 40.7 mg/kg bw/day (SCCS 2016). The critical effect level of 4.1 mg/kg bw/day identified is supported by other studies with similar endpoints, such as an extended one-generation reproduction toxicity study in which the NOAEL was 4.5 mg/kg bw/day based on liver toxicity, decreased food consumption in F0 females and decreased maternal body weights, reduced pup weights, and decreased acetylcholinesterase activity in pups and adolescent rats at the next dose of 15.1 mg/kg bw/day (SCCS 2019).

No suitable hazard data were identified for the dermal and inhalation routes; therefore, the oral NOAEL of 4.1 mg/kg bw/day was used for characterization of risk along with route-to-route extrapolation for aldehydes subgroup 2. Daily exposure estimates for the highest and lowest exposed age groups and resulting MOEs for lilial are summarized in Table 7-26.

Table 7-26. Daily exposure estimates and resulting MOEs for lilial

Exposure scenario	Systemic exposure (mg/kg bw/day)^a	MOE^b
Inhalation and oral exposures from environmental media (that is, air, water, dust, and soil) (all subpopulations)	6.70 x 10 ⁻⁴ (adult) to 2.49 x 10 ⁻³ (1 year)	1 647 (1 year) to 6 119 (adults)
Dermal and inhalation exposures from body fragrance (44%) (2–3 years to adults)	0.54 (adult) to 1.52 (2–3 years)	3 (2–3 years) to 8 (adult)
Dermal and inhalation exposures from liquid body cleanser (1%) (all subpopulations)	3.24 x 10 ⁻³ (adult) to 1.3 x 10 ⁻² (0–5 months)	318 (0–5 months) to 1 265 (adult)
Dermal and inhalation exposures from hair conditioner (wash-off) (2%) (2–3 years to adults)	5.06 x 10 ⁻³ (14–18 years) to 1.06 x 10 ⁻² (2–3 years)	387 (2–3 years) to 810 (14–18 years)
Dermal and inhalation exposures from massage oil (0.3%) (all subpopulations)	2.58 x 10 ⁻² (adult) to 1.38 x 10 ⁻¹ (0–5 months)	30 (0–5 months) to 159 (adults)
Dermal and inhalation exposures from body moisturizer (1%) (all subpopulations)	2.17 x 10 ⁻¹ (adult) to 4.84 10 ⁻¹ (0–5 months)	8 (0–5 months) to 19 (adults)
Dermal and inhalation exposures from liquid face makeup (1%) (4–8 years to adults)	1.30 x 10 ⁻² (14–18 years) to 2.69 x 10 ⁻² (4–8 years)	152 (4–8 years) to 315 (14–18 years)
Dermal and inhalation exposures from nail polish product (3%) (2–3 years to adults)	9.73 x 10 ⁻³ (adult) to 1.80 x 10 ⁻² (2–3 years)	228 (2–3 years) to 421 (adult)
Dermal and inhalation exposures from a nail polish remover product (0.1%) (2–3 years to adults)	5.86 x 10 ⁻³ (adult) to 1 x 10 ⁻² (9–13 years)	405 (9–13 years) to 700 (adult)
Dermal and inhalation exposures from depilator product (0.1%) (9–13 years to adults)	3.67 x 10 ⁻³ (14–18 years) to 4.46. x 10 ⁻³ (adult)	920 (adult) to 1 117 (14–18 years)
Dermal and inhalation exposures from solid antiperspirant/deodorant (3%) (9–13 years to adults)	5.18 x 10 ⁻² (9–13 years) to 8.63 x 10 ⁻² (14–18 years)	48 (14–18 years) to 79 (9–13 years)
Dermal and inhalation exposures from spray antiperspirant/deodorant (0.3%) (9–13 years to adults)	1.01 x 10 ⁻² (9–13 years) to 2.67 x 10 ⁻² (14–18 years)	153 (14–18 years) to 406 (9–13 years)
Dermal and inhalation exposures from bath product (3%) (all subpopulations)	9.18 x 10 ⁻⁴ (9–13 years) to 2.83 x 10 ⁻³ (14–18 years)	1 451 (14–18 years) to 4 464 (9–13 years)
Dermal and inhalation exposures from facial moisturizer (3%) (9–13 years to adults)	1.32 x 10 ⁻¹ (14–18 years) to 2.11 x 10 ⁻¹ (adult)	19 (adult) to 31 (14–18 years)

Exposure scenario	Systemic exposure (mg/kg bw/day)^a	MOE^b
Dermal and inhalation exposures from permanent hair colour product (1%) (14–18 years to adults)	2.69 x 10 ⁻¹ (adult) to 3.21 x 10 ⁻¹ (14–18 years)	13 (14–18 years) to 15 (adult)
Dermal and inhalation exposures from temporary hair colour product (0.11%) (4–8 years to adults)	8.33 x 10 ⁻³ (adult) to 2.59 x 10 ⁻² (4–8 years)	158 (4–8 years) to 492 (adult)
Dermal and inhalation exposures from hair straightening, waving, and curling product (1%) (4–8 years to adults)	1.62 x 10 ⁻¹ (adult) to 4.31 x 10 ⁻¹ (4–8 years)	10 (4–8 years) to 25 (adult)
Dermal and inhalation exposures from lotion sunless tanning product for the face (non-SPF) (1%) (14–18 years to adults)	3.35 x 10 ⁻² (adult) to 3.94 x 10 ⁻² (14–18 years)	104 (14–18 years) to 123 (adult)
Dermal and inhalation exposures from acne treatment (0.11%) (NHP) (9–13 years to adults)	2.23 x 10 ⁻⁴ (adult) to 3.53 x 10 ⁻⁴ (9–13 years)	11 610 (9–13 years) to 18 412 (adults)
Dermal and inhalation exposures from antiseptic skin cleanser product (0.007%) (NHP) (2–3 years to adults)	3.56 x 10 ⁻⁴ (14–18 years) to 1.05 x 10 ⁻³ (2–3 years)	3 904 (2–3 years) to 11 516 (14–18 years)
Dermal and inhalation exposures from antiseptic skin cleanser product ^c (0.007%) (NHP) (2–3 years to adults)	5.33 x 10 ⁻³ (adult) to 2.63 x 10 ⁻² (2–3 years)	156 (2–3 years) to 770 (adults)
Dermal and inhalation exposures from carpet deodorizer (application) (1%) (adults)	7.71 x 10 ⁻⁴ (adult)	5 316 (adult)
Dermal, inhalation, and incidental oral post-application exposures from carpet deodorizer (1%) (1 year)	1.31 x 10 ⁻² (1 year)	312 (1 year)
Inhalation exposure from solid gel air freshener (5%) (all subpopulations)	5.31 x 10 ⁻² (adult) to 2.11 x 10 ⁻¹ (1 year)	19 (1 year) to 77 (adults)
Inhalation exposure from liquid plug-in air freshener (3%) (all subpopulations)	1.37 x 10 ⁻² (adult) to 4.87 x 10 ⁻² (1 year)	84 (1 year) to 300 (adults)

^a Exposure scenario parameters and calculations for aldehydes subgroup 2 are outlined in Appendix A. Dermal absorption was assumed to be 15%.

^b MOEs were calculated using the critical effect level (NOAEL = 4.1 mg/kg bw/day) based on a developmental toxicity study in rats.

^c For situations of public health concern, the use of hand sanitizers among the general population may increase up to 25 uses per day (personal use by adults, increased use by children in schools and child care facilities) (RIVM 2021a).

The MOEs between the critical effect level and the estimates of exposure to lilial from environmental media, body cleanser, hair conditioner, massage oil (9 years and older), liquid face makeup, nail polish, nail polish remover, depilator product, spray antiperspirant/deodorant, bath product, acne treatment cream (NHP), antiseptic skin cleanser (NHP), temporary hair colour, facial sunless tanning product, and carpet deodorizer are considered to be adequate to account for uncertainties in the health effects and exposure data used to characterize risk.

The MOEs between the critical effect level and the estimates of daily exposure to lilial from cosmetics,¹³ solid gel air freshener, and a liquid plug-in air freshener (1 year old) are below 100, which account for uncertainties with respect to interspecies extrapolation, intraspecies extrapolation, the POD, and the adequacy of the database and are considered potentially inadequate.

In addition, daily exposure estimates for the highest and lowest exposed age groups and resulting MOEs for lilial, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde are summarized in Table 7-27.

Table 7-27. Daily exposure estimates and resulting MOEs for lilial, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde

Exposure scenario	Systemic exposure (mg/kg bw/day) ^a	MOE ^b
Dermal and inhalation exposures from leave-on cosmetics (0.05%) (all subpopulations)	1.08 x 10 ⁻¹ (adults) to 2.42 x 10 ⁻² (0–5 months)	169–379
Dermal and inhalation exposures from rinse-off cosmetics (0.1%) (all subpopulations)	1.71 x 10 ⁻³ (adults) to 4.37 x 10 ⁻³ (0–5 months)	938–2 400
Inhalation exposure from air fresheners product (2.5 %) (all subpopulations)	1.14 x 10 ⁻² (adults) to 4.07 x 10 ⁻² (1 year)	101
Dermal and inhalation exposures from cleaning products (0.05%) (all subpopulations)	1.66 x 10 ⁻⁵ (14–18 years) to 5.6 x 10 ⁻⁴ (adults)	7 300–200 000

^a Exposure scenario parameters and calculations for aldehydes subgroup 2 are outlined in Appendix A. Dermal absorption was assumed to be 15%.

^b MOEs were calculated using the critical effect level (NOAEL = 4.1 mg/kg bw/day) based on a developmental toxicity study in rats.

The MOEs between the critical effect level and the estimates of exposure to lilial, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde from cosmetics, air fresheners, and cleaning products are considered to

¹³ Cosmetics refers to body fragrance, massage oil (up to 8 years old), body moisturizer, solid antiperspirant/deodorant, facial moisturizer, permanent hair colour product, and hair straightening, waving and curling product.

be adequate to account for uncertainties in the health effects and exposure data used to characterize risk.

Since there were no identified sources of exposure to verdantiol for the general population, a qualitative approach to risk characterization was taken, and the risk to human health from verdantiol was considered to be low.

While exposure of the general population to myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, vernaldehyde, and verdantiol are not of concern at current levels, these substances are considered to present a health effect of concern based on their potential reproductive and developmental toxicity. Therefore, there may be a concern if exposures were to increase.

7.5.4 Uncertainties in evaluation of risk to human health

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

Table 7-28. Sources of uncertainty in the risk characterization for aldehydes subgroup 2

Key source of uncertainty	Impact
The potential use of more than one product by a single person in a day (that is, aggregate exposure) was not considered. This may potentially underestimate exposure to some individuals.	-
The use of multiple aldehydes subgroup 2 substances in the same product was not considered. However, maximum concentrations were used in the risk assessment, which may be representative of the sum of multiple substances.	-
There are no hazard data available for myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, or vernaldehyde. The read-across analogue and a member of aldehydes subgroup 2, lilial, was used to inform risk assessment.	+/-
Route-to-route extrapolation for aldehydes subgroup 2 was carried out for dermal and inhalation exposure scenarios using a critical effect level from an oral toxicity study.	+/-

+ = uncertainty with potential to cause overestimation of exposure/risk; - = uncertainty with potential to cause underestimation of exposure risk; +/- = unknown potential to cause over- or underestimation of risk

8. Consideration of subpopulations who may have greater susceptibility or exposure

There are groups of individuals within the Canadian population who, due to greater susceptibility or greater exposure, may be more vulnerable to experiencing adverse health effects from exposure to substances. Certain populations are routinely considered throughout the assessment process, such as infants, children, and people of

reproductive age. For instance, age-specific exposures are routinely estimated, and developmental and reproductive toxicity studies are evaluated for potential adverse health effects. These subpopulations with potential for higher exposure and those who may be more susceptible were taken into account in the risk assessment outcomes.

9. Conclusion

Considering all available lines of evidence presented in this draft assessment, there is low risk of harm to the environment from the substances in the Phenylpropanoids and Aldehydes Group. It is proposed to conclude that the 12 substances in the Phenylpropanoids and Aldehydes 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 assessment, it is proposed to conclude that bay oil, tarragon oil, jasmine oil, perfumes and essences of jasmin, violet oil, and lilial 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, and that verdantiol, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde do not meet the criteria under paragraph 64(c) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore proposed to conclude that bay oil, tarragon oil, jasmine oil, perfumes and essences of jasmin, violet oil, and lilial meet one or more of the criteria set out in section 64 of CEPA and that verdantiol, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, and vernaldehyde do not meet any of the criteria set out in section 64 of CEPA.

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

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Appendix A. Parameters for estimating oral, dermal, and inhalation exposures to products available to consumers

Exposures to products available to consumers were estimated using ConsExpo Web (RIVM 2018). Exposure estimates were calculated using default body weights and inhalation rates of 74 kg/15.1 m³/day for adults (19 years and older); 62 kg/15.9 m³/day for 14- to 18-year-olds; 42 kg/13.9 m³/day for 9- to 13-year-olds; 23 kg/11.1 m³/day for 4- to 8-year-olds; 15 kg/9.2 m³/day for 2- to 3-year-olds; 11 kg/8.0 m³/day for 1-year-olds; 9.1 kg/5.4 m³/day for 6- to 11-month-olds; and 6.3 kg/3.7 m³/day for 0- to 5-month-olds (HC 2019b).

A dermal absorption factor of 20% was used for violet oil, 50% for phenylpropanoids subgroup 1 (jasmine oil, perfumes and essences of jasmin), 40% for bay oil and tarragon oil, and 15% for substances in aldehydes subgroup 2 (lilial, myrac-aldehyde, myrmac-aldehyde, myrmac-carboxaldehyde, cetonal, vernaldehyde). Calculated exposure estimates for violet oil and bay oil were adjusted by 19% and 2% for the maximum amount of 2,6-nonadienal and methyl eugenol in violet oil and bay oil, respectively.

When calculating the LADDs, an average lifetime of 78 years was used (HC 2013).

Table A-1. Parameters for estimating dermal, inhalation, and oral exposures to products available to consumers

Exposure scenario	Assumptions
Eye moisturizer (violet oil)	<p>Concentration: 100% violet oil</p> <p>Product amount: 0.16 g (adults and 14–18 yrs) (Ficheux et al. 2016). Frequency: 1 (Ficheux et al. 2015)</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model. Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance. Exposure and emission duration: 24 hours Molecular weight matrix: 1000 g/mol Temperature: 32°C Room volume: 58 m³ Ventilation rate: 0.5/h Surface area: 50 cm² (surface area of eye area) (Bremmer et al. 2006)</p>

Exposure scenario	Assumptions
	<p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
Hair conditioner (leave-on) (violet oil, bay oil)	<p>Concentration: 100% violet oil, 3% bay oil (assuming the 0.0002% maximum concentration of methyl eugenol permitted according to the Cosmetic Ingredient Hotlist)</p> <p>Product amount (violet oil): 1.5 g, assumed for all the subpopulations (as per manufacturer instructions)</p> <p>Product amount (bay oil): 13.1 g (adults); 10 g (14–18 yrs); 7.8 g (9–13 yrs and 4–8 yrs); 5.2 g (2–3 yrs) (Ficheux et al. 2016; Garcia-Hidalgo et al. 2017)</p> <p>Frequency: 1.1 (adults) (Loretz et al. 2008). For all other subpopulations, the mean frequency was assumed to be 1.</p> <p>Retention factor: 0.1</p> <p>Bay oil dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * retention factor * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p> <p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance. For adults, product amount was increased to account for a frequency of 1.1 per day.</p> <p>Exposure and emission duration: 24 h</p> <p>Molecular weight matrix: pure substance (100%) (violet oil)</p> <p>Molecular weight matrix: 1000 g/mol (bay oil)</p> <p>Temperature: 32°C</p> <p>Room volume: 58 m³</p> <p>Ventilation rate: 0.5/h</p> <p>Surface area: surface area of the scalp. 1040 cm² (adults); 755 cm² (14–18 yrs); 655 cm² (9–13 yrs); 520 cm² (4–8 yrs); 275 cm² (2–3 yrs)</p>

Exposure scenario	Assumptions
	<p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Bay oil: combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p> <p>A lifetime average daily dose (LADD) was also calculated for bay oil using the following formula:</p> <p>LADD (mg/kg bw/day) = ((combined exposure (mg/kg bw/day) 0–5 mths * time in lifestage (0.5 yr)) + (combined exposure (mg/kg bw/day) 6–12 mths * time in lifestage (0.5 yr)) + (combined exposure (mg/kg bw/day) 1 yr * time in lifestage (1 yr)) + (combined exposure (mg/kg bw/day) 2–3 yrs * time in lifestage (2 yrs)) + (combined exposure (mg/kg bw/day) 4–8 yrs * time in lifestage (5 yrs)) + (combined exposure (mg/kg bw/day) 9–13 yrs * time in lifestage (5 yrs)) + (combined exposure (mg/kg bw/day) 14–18 yrs * time in lifestage (5 yrs)) + (combined exposure (mg/kg bw/day) adult (19+) * time in lifestage (59 yrs)))/Average lifetime (78 yrs)</p>
Hair conditioner (wash-off) (jasmine oil, lilial)	<p>Concentration: 30% jasmine oil, 2% lilial.</p> <p>Product amount (jasmine oil): 0.71 g, assumed for all the subpopulations (personal communication, email communication from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, February 2021; unreferenced)</p> <p>Product amount (lilial): 13.1 g (adults); 10 g (14–18 yrs); 7.8 g (9–13 yrs and 4–8 yrs); 5.2 g (2–3 yrs) (Ficheux et al. 2016; Garcia-Hidalgo et al. 2017)</p> <p>Frequency: 1.1 (adults) (Loretz et al. 2008). For all other subpopulations, the mean frequency was assumed to be 1. Retention factor: 0.01</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal</p>

Exposure scenario	Assumptions
	<p>absorption * retention factor * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p> <p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance. For adults, product amount was increased to account for a frequency of 1.1 per day.</p> <p>Exposure and emission duration (jasmine oil): 1 h (as per manufacturer instructions)</p> <p>Exposure and emission duration (lilial): 5 min</p> <p>Molecular weight matrix: 1000 g/mol</p> <p>Temperature: 32°C</p> <p>Room volume: 10 m³</p> <p>Ventilation rate: 2/h</p> <p>Surface area: surface area of the scalp. 1040 cm² (adults); 755 cm² (14–18 yrs); 655 cm² (9–13 yrs); 520 cm² (4-8 yrs); 275 cm² (2–3 yrs)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
Facial cleanser (violet oil, tarragon oil)	<p>Concentration: 30% violet oil, 0.1% tarragon oil</p> <p>Product amount: 3.3 g (adults and 14–18 yrs); 3.1 g (9–13 yrs) (Ficheux et al. 2016)</p> <p>Frequency: 1.6/day (adults) (Loretz et al. 2008); 1.2/day (14–18 yrs and 9–13 yrs) (Ficheux et al. 2015)</p> <p>Retention factor: 0.01</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * retention factor * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p>

Exposure scenario	Assumptions
	<p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance and the retention factor.</p> <p>Exposure and emission duration: 5 min</p> <p>Molecular weight matrix: 1000 g/mol</p> <p>Temperature: 32°C</p> <p>Room volume: 10 m³</p> <p>Ventilation rate: 2/h</p> <p>Surface area: surface area of half head, 585 cm² (adults); 370 cm² (14–18 yrs); 350 cm² (9–13 yrs)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p> <p>For tarragon oil, a LADD was also calculated using the following formula :</p> <p>LADD (mg/kg bw/day) = {[combined exposure (mg/kg bw/day) 9–13 yrs * time in lifestage (5 yrs)] + [combined exposure (mg/kg bw/day) 14–18 yrs * time in lifestage (5 yrs)] + [combined exposure (mg/kg bw/day) adult (19+) * time in lifestage (59 yrs)]} / Average lifetime (78 yrs)</p>
Acne treatment (NHP) (lilial)	<p>Concentration: 0.1% lilial</p> <p>Product amount: 3.3 g (adults and 14–18 yrs); 3.1 g (9–13 yrs) (Ficheux et al. 2016)</p> <p>Frequency: 3/day (all subpopulations) (as per manufacturer recommendation)</p> <p>Retention factor: 0.01</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * retention factor * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p>

Exposure scenario	Assumptions
	<p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance and the retention factor.</p> <p>Exposure and emission duration: 15 h (adults); 20 h (14–18 yrs and 9–13 yrs)</p> <p>Molecular weight matrix: 1000 g/mol</p> <p>Temperature: 32°C</p> <p>Room volume: 20 m³</p> <p>Ventilation rate: 0.6/h</p> <p>Surface area: surface area of half head, 585 cm² (adults); 370 cm² (14–18 yrs); 350 cm² (9–13 yrs)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
<p>Body moisturizer (violet oil, bay oil, tarragon oil, jasmine oil, and lilial)</p>	<p>Concentration: 10% violet oil, 0.3% bay oil (assuming the 0.002% maximum concentration of methyl eugenol permitted according to the Cosmetic Ingredient Hotlist), 0.3% tarragon oil, 3% jasmine oil, 1% lilial, 0.1% fragrance ingredient</p> <p>Product amount: 10 g (adults and 14–18 yrs); 7.7 g (9–13 yrs); 5 g (4–8 yrs); 4.1 g (2–3 yrs); 3.1 g (1 yr); 2.5 g (6–11 mths); 2 g (0–5 mths) (Ficheux et al. 2016)</p> <p>Frequency: 1 (adults) (Wu et al. 2010; Ficheux et al. 2015).</p> <p>For all other subpopulations, the mean frequency was assumed to be 1.</p> <p>For bay oil and tarragon oil (calculation of LADD), a frequency of 0.8/day was used for all other subpopulations (Wu et al. 2010; Ficheux et al. 2015).</p> <p>For bay oil, tarragon oil, jasmine oil, and lilial, dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency (1/day) * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p>

Exposure scenario	Assumptions
	<p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p> <p>Product amount: adjusted for unclothed surface area of short-sleeved shirt and shorts. 4.87 g (adults); 4.65 g (14–18 yrs); 3.61 g (9–13 yrs); 2.3 g (4–8 yrs); 1.85 g (2–3 yrs); 1.45 g (1 yr); 1.16 g (0–5 mths); 0.93 g (0–5 mths).</p> <p>Exposure and emission duration: 24 h Molecular weight matrix: 1000 g/mol Temperature: 32°C Room volume: 58 m³ Ventilation rate: 0.5/h Surface area: equivalent to arms, ¾ legs, hands, and ½ feet (short-sleeved shirt and shorts). 8543 cm² (adults); 7655 cm² (14–18 yrs); 5953 cm² (9–13 yrs); 3813 cm² (4–8 yrs); 2685 cm² (2–3 yrs); 2070 cm² (1 yr); 1703 cm² (6–11 mths); 1325 cm² (0–5 mths)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day) * Frequency (calculation of LADD only)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p> <p>For bay oil and tarragon oil, LADDs were also calculated using the following formula (HC 2013):</p> <p>LADD (mg/kg bw/day) = ((combined exposure (mg/kg bw/day) 0–5 mths * time in lifestage (0.5 yr)) + (combined exposure (mg/kg bw/day) 6–12 mths * time in lifestage (0.5 yr)) + (combined exposure (mg/kg bw/day) 1 yr * time in lifestage (1 yr)) + (combined exposure (mg/kg bw/day) 2–3 yrs * time in lifestage (2 yrs)) + (combined exposure (mg/kg bw/day) 4–8 yrs * time in lifestage (5 yrs)) + (combined exposure (mg/kg bw/day) 9–13 yrs * time in lifestage (5 yrs)) + (combined exposure (mg/kg bw/day) 14–18 yrs * time in lifestage (5 yrs)) + (combined exposure (mg/kg bw/day) adult (19+) * time in lifestage (59 yrs)))/Average lifetime (78 yrs)</p>
Massage oil (violet oil, lillial)	Concentration: 10% violet oil, 0.3% lillial.

Exposure scenario	Assumptions
	<p>Product amount: 3.2 g (adults); 2.9 g (14–18 yrs); 2.3 g (9–13 yrs); 1.9 g (4–8 yrs); 1.8 g (2–3 yrs, 1 yr, 6–11 mths, 0–5 mths) (Ficheux et al. 2016)</p> <p>Frequency: assumed to be 1 for all subpopulations.</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p> <p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance.</p> <p>Exposure and emission duration: 24 h</p> <p>Molecular weight matrix: 1000 g/mol</p> <p>Temperature: 32°C</p> <p>Room volume: 58 m³</p> <p>Ventilation rate: 0.5/h</p> <p>Surface area: equivalent to total surface area minus half head and half trunk for adults and 14–18 yrs, and total surface area minus half head for all other subpopulations. 8543 cm² (adults); 7655 cm² (14–18 yrs); 5953 cm² (9–13 yrs); 3813 cm² (4–8 yrs); 2685 cm² (2–3 yrs); 2070 cm² (1 yr); 1703 cm² (6–11 mths); 1325 cm² (0–5 mths)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
Lipstick (violet oil, jasmine oil)	<p>Concentration: 10% violet oil, 3% jasmine oil</p> <p>Product amount: 0.022 g (all subpopulations) (Ficheux et al. 2016)</p> <p>Frequency: 2 (adults); 2.5 (14–18 yrs); 1.2 (9–13 yrs and 4–8 yrs); 1 (2–3 yrs) (Statistics Canada 2017)</p> <p>Oral exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean</p>

Exposure scenario	Assumptions
Body fragrance (violet oil, bay oil, tarragon oil, jasmine oil, lilial)	<p data-bbox="581 247 1414 310">daily frequency (1/day) * product concentration * conversion factor (mg/g)] ÷ Body weight</p> <p data-bbox="581 317 1414 499">Concentration: 10% violet oil, 10% bay oil (assuming 0.004% for eau de toilette and 0.01% for fine fragrance as the maximum concentration of methyl eugenol permitted according to the Cosmetic Ingredient Hotlist), 100% tarragon oil, 82% jasmine oil, 44% lilial</p> <p data-bbox="581 537 1414 600">Product amount: based on eaux de toilette, 0.33 g (adults, 14–18 yrs, and 9–13 yrs) (Ficheux et al. 2016)</p> <p data-bbox="581 646 1414 709">Frequency: 1.7/day (adults) (Loretz et al. 2006); 1.4/day (14–18 yrs and 9–13 yrs) (Statistics Canada 2017)</p> <p data-bbox="581 793 1414 976">For bay oil, tarragon oil, jasmine oil, and lilial, dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p> <p data-bbox="581 1014 1414 1119">For the spray products, air concentrations were modelled using the ConsExpo exposure to spray–evaporation–constant release area model.</p> <p data-bbox="581 1125 1414 1230">Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance and the daily frequency.</p> <p data-bbox="581 1236 1414 1299">Exposure and emission duration: 14 h (adults); 17 h (14–18 yrs and 9–13 yrs)</p> <p data-bbox="581 1306 1414 1337">Spray duration: 0.08 min</p> <p data-bbox="581 1344 1414 1375">Exposure duration: 5 min</p> <p data-bbox="581 1381 1414 1413">Room volume: 10 m³</p> <p data-bbox="581 1419 1414 1451">Room height: 2.5 m</p> <p data-bbox="581 1457 1414 1488">Ventilation rate: 2/h</p> <p data-bbox="581 1495 1414 1526">Cloud volume: 0.0625 m³</p> <p data-bbox="581 1533 1414 1564">Mass generation rate: 0.14 g/s</p> <p data-bbox="581 1570 1414 1602">Airborne fraction: 0.2 g/g</p> <p data-bbox="581 1608 1414 1640">Weight fraction non-volatile: 0.05 g/g/</p> <p data-bbox="581 1646 1414 1677">Density non-volatile: 1.5 g/cm³</p> <p data-bbox="581 1684 1414 1715">Median (C.V): 50 µm</p> <p data-bbox="581 1722 1414 1753">Inhalation cut-off diameter: 15 µm</p> <p data-bbox="581 1785 1414 1881">For the roll-on products, air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p>

Exposure scenario	Assumptions
	<p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance and the daily frequency. Exposure and emission duration: 14 h (adults); 17 h (14–18 yrs and 9–13 yrs) Molecular weight matrix: 1000 g/mol Temperature: 32°C Room volume: 58 m³ Ventilation rate: 0.5/h Surface area: 100 cm² (all subpopulations) (application to 25 cm² in 4 places)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p> <p>For bay oil and tarragon oil, LADDs were also calculated using the following formula (HC 2013):</p> <p>LADD (mg/kg bw/day) = ((combined exposure (mg/kg bw/day) 9–13 yrs * time in lifestage (5 yrs)) + (combined exposure (mg/kg bw/day) 14–18 yrs * time in lifestage (5 yrs)) + (combined exposure (mg/kg bw/day) adult (19+) * time in lifestage (59 yrs)))/Average lifetime (78 yrs))</p>
De-stress roll-on (NHP) (jasmine oil)	<p>Concentration: 0.01%</p> <p>Product amount: 0.14 g [as per manufacturer instruction, 0.15 mL * jasmine oil density (0.947 g/mL)]</p> <p>Frequency :3/day (as per manufacturer instructions)</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p>

Exposure scenario	Assumptions
	<p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance and the daily frequency.</p> <p>Exposure and emission duration: 24 h Molecular weight matrix: 1000 g/mol Temperature: 32°C Room volume: 20 m³ Ventilation rate: 0.6/h Surface area: 200 cm²</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
Bath product (lilial)	<p>Concentration: 3% lilial</p> <p>Product amount: For lilial, 0.0394 g (adults), 0.0370 g (14–18 yrs), 0.0078 g (9–13 yrs) (Ficheux et al.2016), 0.051 g (4–8 yrs), 0.0055 g (2–3 yrs), 0.0041 g (1yr), 0.0034 g (6–11 mths) (Garcia-Hidalgo et al. 2017), 0.0026 g (0–5 mths) (Garcia-Hidalgo et al. 2017)</p> <p>Frequency: 1 (all subpopulations)</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * retention factor * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p> <p>Product amount: as above, adjusted to account for the amount systemically absorbed by the dermal route. Exposure and emission duration: 45 min Molecular weight matrix: 18 g/mol Temperature: 32°C Room volume: 10 m³ Ventilation rate: 2/h</p>

Exposure scenario	Assumptions
	<p>Surface area: 11 552 cm² (equivalent to the surface area of a bathtub, standard tub dimensions of 76 cm x 152 cm)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
Facial moisturizer (tarragon oil, lilial)	<p>Concentration: 0.1% tarragon oil, 3% lilial</p> <p>Product amount: 1.5 g (adults and 14–18 yrs); 1.1 g (9–13 yrs) (Ficheux et al. 2016)</p> <p>Frequency: 2/day (adults) (Loretz et al. 2005); 1/day (14–18 yrs and 9–13 yrs) (Ficheux et al. 2015)</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p> <p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance.</p> <p>Exposure and emission duration: 12 h (adults); 24 h (14–18 yrs and 9–13 yrs)</p> <p>Molecular weight matrix: 1000 g/mol</p> <p>Temperature: 32°C</p> <p>Room volume: 20 m³</p> <p>Ventilation rate: 0.6/h</p> <p>Surface area: surface area of half head, 585 cm² (adults); 370 cm² (14–18 yrs); 350 cm² (9–13 yrs)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>

Exposure scenario	Assumptions
	<p>For tarragon oil, a LADD was also calculated using the following formula:</p> $\text{LADD (mg/kg bw/day)} = \{[\text{combined exposure (mg/kg bw/day) 9–13 yrs} * \text{time in lifestage (5 yrs)}] + [\text{combined exposure (mg/kg bw/day) 14–18 yrs} * \text{time in lifestage (5 yrs)}] + [\text{combined exposure (mg/kg bw/day) adult (19+)} * \text{time in lifestage (59 yrs)}]\} / \text{Average lifetime (78 yrs)}$
<p>Facial moisturizer/acne treatment (NHP) (jasmine oil)</p>	<p>Concentration: jasmine oil 1%</p> <p>Product amount: 1.5 g (adults) (Ficheux et al. 2016) Frequency: 3/day (all subpopulations) (as per manufacturer recommendations)</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: $[\text{mean product (g/application)} * \text{mean daily frequency} * \text{product concentration} * \text{dermal absorption} * \text{conversion factor (1000 mg/g)}] \div \text{Body weight}$</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model. Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance. Exposure and emission duration: 12 h (adults) Molecular weight matrix: 1000 g/mol Temperature: 32°C Room volume: 20 m³ Ventilation rate: 0.6/h Surface area: surface area of half head, 585 cm²</p> <p>Inhalation exposure (mg/kg bw/day) = $[\text{Air concentration (mg/m}^3\text{)} (24 \text{ h time-weighted average)} * \text{Inhalation rate (m}^3\text{/day)}] \div \text{Body weight}$</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
<p>Facial sun protection powder (NHP) (jasmine oil)</p>	<p>Concentration: 0.07%</p> <p>Product amount: 0.073 g (adults) (Ficheux et al. 2016)</p>

Exposure scenario	Assumptions
	<p>Frequency: 6/day (as per manufacture recommendations)</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p> <p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance.</p> <p>Exposure duration: 24 h</p> <p>Emission duration: 20 h</p> <p>Molecular weight matrix: 1000 g/mol</p> <p>Temperature: 32°C</p> <p>Room volume: 20 m³</p> <p>Ventilation rate: 0.6/h</p> <p>Surface area: surface area of half-head, 585 cm²</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
<p>Topical treatment cream (NHP) (jasmine oil)</p>	<p>Concentration: 1% jasmine oil</p> <p>Product amount: 1.5 g (adults) (Ficheux et al. 2016)</p> <p>Frequency: 1/day (as per manufacturer recommendations)</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p> <p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance.</p>

Exposure scenario	Assumptions
	<p>Exposure and emission duration: 12 h Molecular weight matrix: 1000 g/mol Temperature: 32°C Room volume: 20 m³ Ventilation rate: 0.6/h Surface area: assuming surface area of the face; 585 cm² (adults)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
Soap (tarragon oil)	<p>Concentration: 0.3% tarragon oil</p> <p>Product amount: 1.1 g (adults and 14–18 yrs), 0.82 g (9–13 yrs), 0.53 g (4–8 yrs), 0.38 g (2–3 yrs), 0.29 g (1 yr), 0.24 g (6–11 mths), 0.18 g (0–5 mths) (Ficheux et al. 2016)</p> <p>Frequency: 1.2 (adults and 14–18 yrs), 1.15 (9–13 yrs and 4–8 yrs), 1.1 (2–3 yrs, 1 yr, 6–11 mths and 0–5 mths) (Ficheux et al. 2015) Retention factor: 0.01</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * retention factor * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model. Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance and to account for a daily frequency of greater than 1.</p> <p>Exposure and emission duration: 5 min Molecular weight matrix: 1000 g/mol Temperature: 32°C Room volume: 10 m³ Ventilation rate: 2/h</p>

Exposure scenario	Assumptions
	<p>Surface area: surface area of total body. 17 530 cm² (adults), 16 460 cm² (14–18 yrs), 12 700 cm² (9–13 yrs), 8 290 cm² (4–8 yrs), 5 950 cm² (2–3 yrs), 4 430 cm³ (1 yr), 3 680 cm² (6–11 mths), 2 860 cm² (0–5 mths)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>LADD was also calculated using the following formula:</p> <p>LADD (mg/kg bw/day) = {[combined exposure (mg/kg bw/day) 0–5 mths * time in lifestage (0.5 yr)] + [combined exposure (mg/kg bw/day) 6–12 mths * time in lifestage (0.5 yr)] + [combined exposure (mg/kg bw/day) 1 yr * time in lifestage (1 yr)] + [combined exposure (mg/kg bw/day) 2–3 yrs * time in lifestage (2 yrs)] + [combined exposure (mg/kg bw/day) 4–8 yrs * time in lifestage (5 yrs)] + [combined exposure (mg/kg bw/day) 9–13 yrs * time in lifestage (5 yrs)] + [combined exposure (mg/kg bw/day) 14–18 yrs * time in lifestage (5 yrs)] + [combined exposure (mg/kg bw/day) adult (19+) * time in lifestage (59 yrs)]}/Average lifetime (78 yrs)</p>
Digestive aid capsule (NHP) (tarragon oil)	<p>Tarragon oil: 0.0026%</p> <p>Product amount: 120 mg (each capsule) (adults)</p> <p>Oral exposure (mg/kg bw/day) was calculated using the following formula: [product amount * concentration * dose frequency (3 per day)] ÷ Body weight</p> <p>LADD was also calculated using the following formula (HC 2013):</p> <p>LADD (mg/kg bw/day) = [oral exposure (mg/kg bw/day) adult (19+) * time in lifestage (59 yrs)]/Average lifetime (78 yrs)</p>
Inhaler stick (NHP) (bay oil)	<p>Concentration: 0.06% bay oil</p> <p>Product amount: 1 g (adults) (calculated assuming the entire product of 1 mL is used in one day and assuming a density of 1 g/mL (1 mL * 1 g/mL)</p> <p>Frequency: it is assumed that a user would use the product 30 days per year (professional judgment)</p>

Exposure scenario	Assumptions
	<p>Inhalation exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * adjusted composition factor (2%) * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>For bay oil, LADD was also calculated using the following formula:</p> <p>LADD (mg/kg bw/day) = [inhalation exposure (mg/kg bw/day) adult (19+) * time in lifestage (59 yrs)]/Average lifetime (78 yrs)</p>
Respiratory air spray (NHP) (bay oil)	<p>Concentration: 2% bay oil</p> <p>Air concentrations were modelled using the exposure to spray–instantaneous release model.</p> <p>Product amount: 1.3 g, 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 9. Mean product amount (g/day) = 0.16 mL/spray (O.Berk Leaders in Packaging Solutions [date unknown]) * 9 sprays/day (manufacturer instructions) * methyl eugenol density (0.9 g/mL) = 1.3 g/day</p> <p>Exposure duration: 240 min (RIVM 2006) Room volume: 58 m³ (RIVM 2006) Ventilation rate: 0.5/h (RIVM 2006) Emission duration: 180 min (RIVM 2006)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day) * Frequency (calculation of LADD only) (168 times/365 (year) based on 14 times per month) (RIVM 2006)] ÷ Body weight</p> <p>LADD was also calculated using the following formula:</p> <p>LADD (mg/kg bw/day) = [inhalation exposure (mg/kg bw/day) adult (19+) * time in lifestage (59 yrs)]/Average lifetime (78 yrs)</p>

Exposure scenario	Assumptions
<p>Antiperspirant/deodorant (solid) (tarragon oil, jasmine oil, lilial)</p>	<p>Concentration: 1% tarragon oil, 2% jasmine oil, 3% lilial</p> <p>Product amount: 1 g (adults and 14–18 yrs); 0.4 g (9–13 yrs) (Ficheux et al. 2016)</p> <p>Frequency: 1.3 (adults) (Loretz et al. 2006); 1.1 (14–18 yrs and 9–13 yrs) (Wu et al. 2010; Ficheux et al. 2015)</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p> <p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance. Product amount was increased to account for frequencies.</p> <p>Exposure and emission duration: 18 h (adults); 22 h (14–18 yrs and 9–13 yrs)</p> <p>Molecular weight matrix: 1000 g/mol</p> <p>Temperature: 32°C</p> <p>Room volume: 58 m³</p> <p>Ventilation rate: 0.5/h</p> <p>Surface area: surface area of underarms. 240 cm² (adults); 234 cm² (14–18 yrs); 179 cm² (9–13 yrs)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p> <p>For tarragon oil, a LADD was also calculated using the following formula:</p> <p>LADD (mg/kg bw/day) = {[combined exposure (mg/kg bw/day) 9–13 yrs * time in lifestage (5 yrs)] + [combined exposure (mg/kg bw/day) 14–18 yrs * time in lifestage (5 yrs)] + [combined exposure (mg/kg bw/day) adult (19+) * time in lifestage (59 yrs)]}/Average lifetime (78 yrs)</p>

Exposure scenario	Assumptions
Antiperspirant/deodorant (spray) (lilial)	<p>Concentration: 0.3% lilial</p> <p>Product amount: 3.48 g (adults and 14–18 yrs) (Hall et al. 2007); 0.98 g (9–13 yrs) (Ficheux et al. 2016)</p> <p>Frequency: 1.3 (adults) (Loretz et al. 2006); 1.2 (14–18 yrs) (Ficheux et al. 2015); 1.1 (9–13 yrs) (Wu et al. 2010)</p> <p>Retention factor: 0.85</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * retention factor * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Inhalation exposure to the spray was quantified using the exposure–spray model–instantaneous release and the following parameters: Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance. Exposure duration: 5 min Room volume: 10 m³ Ventilation rate: 2/h</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
Antiseptic skin cleanser (NHP) (jasmine oil, lilial)	<p>Concentration: 2% jasmine oil, lilial 0.07%</p> <p>Product amount: 1.5 g (all age groups, Kampf et al. 2013; Macinga et al. 2013; Bánsághi et al. 2020)</p> <p>Frequency: 2.9 (adults); 1.4 (14–18 yrs, 9–13 yrs, 4–8 yrs), 0.8 (adjusted to 1) (2– 3 yrs) (Wu et al. 2010)</p> <p>Frequency (for situations of public health concern): 25/day (all age groups, RIVM 2021a)</p>

Exposure scenario	Assumptions
	<p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant rate release model.</p> <p>Exposure and emission duration: 20 min (all age groups) Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance. Room volume: 20 m³ Ventilation rate: 0.6/h Temperature: 32°C</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
<p>Body cleanser (liquid) (bay oil, jasmine oil, lillial)</p>	<p>Concentration: 3% bay oil (assuming the 0.001% maximum concentration of methyl eugenol permitted according to the Cosmetic Ingredient Hotlist), 3% jasmine oil, 1% lillial</p> <p>Product amount: 11 g (adults and 14–18 yrs); 10.9 g (9–13 yrs and 4–8 yrs); 6.7 g (2–3 yrs); 5.4 g (1 yr); 4.9 g (6–11 mths); 4.5 g (0–5 mths) (Loretz et al. 2006; Ficheux et al. 2016; Garcia-Hidalgo et al. 2017)</p> <p>Frequency: 1.4 (adults); 1.2 (14–18 yrs, 2–3 yrs, 1 yr, 6–11 mths, and 0–5 mths); 1 (9–13 yrs and 4–8 yrs) (Loretz et al. 2006; Ficheux et al. 2015).</p> <p>Frequencies less than 1 were assigned a frequency of 1.</p> <p>Retention factor: 0.01</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean</p>

Exposure scenario	Assumptions
	<p>daily frequency * product concentration * dermal absorption * retention factor * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p> <p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance.</p> <p>Exposure and emission duration: 5 min</p> <p>Molecular weight matrix: 1000 g/mol</p> <p>Temperature: 32°C</p> <p>Room volume: 10 m³</p> <p>Ventilation rate: 2/h</p> <p>Surface area: equivalent to arms, ¾ legs, hands, and ½ feet (short-sleeved shirt and shorts). 17 530 cm² (adults); 16 460 cm² (14–18 yrs); 12 700 cm² (9–13 yrs); 8 290 cm² (4–8 yrs); 5 950 cm² (2–3 yrs); 4 430 cm² (1 yr); 3 680 cm² (6–11 mths); 2 860 cm² (0–5 mths)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
Permanent hair colour (lilial)	<p>Concentration: 1% lilial</p> <p>Product amount: 132.6 g (adults and 14–18 yrs) (Ramirez-Martinez et al. (2015))</p> <p>Retention factor: 0.1</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * retention factor * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p> <p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance.</p>

Exposure scenario	Assumptions
	<p>Exposure and emission duration: 1.5 h Molecular weight matrix: 1000 g/mol Temperature: 32°C Room volume: 10 m³ Ventilation rate: 2/h Mass transfer coefficient: 10 m/h Surface area: equivalent to half head, 585 cm² (adult); 370 cm² (14–18 yrs)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
Temporary hair colour (jasmine oil, lillial)	<p>Concentration: 0.1% jasmine oil, 0.11% lillial</p> <p>Product amount: 35 g (adults, 14–18 yrs, 9–13 yrs, and 4–8 yrs) (SCCS 2015) Retention factor: 0.1</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * retention factor * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model. Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance. Exposure and emission duration: 24 h, all subpopulations Molecular weight matrix: 1000 g/mol Temperature: 32°C Room volume: 58 m³ Ventilation rate: 0.5/h Surface area: equivalent to half head, 585 cm² (adult); 370 cm² (14–18 yrs); 350 cm² (9–13 yrs), 305 cm² (4–8 yrs) Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p>

Exposure scenario	Assumptions
	<p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
<p>Aerosol hair styling product (jasmine oil)</p>	<p>Concentration: 0.1% jasmine oil</p> <p>Product amount: 2.6 g (adults) (Loretz et al. 2008); 2.3 g (14–18 yrs, 9–13 yrs, and 4–8 yrs) (Ficheux et al. 2016) Frequency: 1.49 (adults) (Loretz et al. 2008). A frequency of 1 was assumed for all other subpopulations. Retention factor: 0.085</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * retention factor * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Inhalation exposure to the spray was quantified using the exposure–spray model–spraying towards exposed person and the following parameters: Spray duration: 0.108 min for adults and 0.096 min for all other subpopulations (based on product amount of 2.6 g (2.6 g/0.4 g/s = 6.5 seconds) (adults) and (2.3 g/0.4 g/s = 5.75 seconds) (all other subpopulations)) Exposure duration: 5 min Room volume: 10 m³ Room height: 2.5 m Ventilation rate: 2/h Cloud volume: 0.0625 m³ Mass generation rate: 0.4 g/s Airborne fraction: 0.15 (mass balance to account for fraction landing on the head 100%–85%) Weight fraction non-volatile: 0.03 g/g Density non-volatile: 1.5 g/cm³ Initial particle distribution: lognormal Median (CV): 46.5 µm (2.1) Inhalation cut-off value: 10 µm</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p>

Exposure scenario	Assumptions
	<p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
<p>Hair straightening, waving, and curling product (lilial)</p>	<p>Concentration: 11% lilial</p> <p>Product amount: 80 g (adults and 14–18 yrs) (Bremmer et al. 2006), 76 g (9–13 yrs) (SA adjustment), 66 g (4–8 yrs) (SA adjustment) Retention factor: 0.1</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * retention factor * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model. Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance. Exposure and emission duration: 0.5 h, all subpopulations Molecular weight matrix: 1000 g/mol Temperature: 32°C Room volume: 34 m³ Ventilation rate: 2/h Surface area: equivalent to half head, 585 cm² (adult); 370 cm² (14–18 yrs); 350 cm² (9–13 yrs), 305 cm² (4–8 yrs)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
<p>Hair removal/depilator (lilial)</p>	<p>Concentration: 0.1% lilial</p> <p>Product amount: 9.7 g (adults, 14–18 yrs and 9–13 yrs); face mask was used as a surrogate, and amount was adjusted for surface area (Ficheux et al. 2016). Retention factor: 0.01</p>

Exposure scenario	Assumptions
	<p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * retention factor * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p> <p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance.</p> <p>Exposure and emission duration: 24 h</p> <p>Molecular weight matrix: 1000 g/mol</p> <p>Temperature: 32°C</p> <p>Room volume: 58 m³</p> <p>Ventilation rate: 0.5/h</p> <p>Surface area: equivalent to legs, 5970 cm² (adults); 5140 cm² (14–18 yrs); 3990 cm² (9–13 yrs)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
Sunscreen (NHP) (jasmine oil, lilial)	<p>Concentration: 0.07% jasmine oil, 0.01% lilial</p> <p>Product amount: 18.2 g (adults and 14–18 yrs); 6.3 g (9–13 yrs and 4–8 yrs); 5.4 g (2–3 yrs, 1 yr, and 6–11 mths) (Ficheux et al. 2016)</p> <p>Frequency: 1.4 (adults, 14–18 yrs, 9–13 yrs, and 4–8 yrs); 1.6 (2–3 yrs, 1 yr, and 6–11 mths) (Ficheux et al. 2015)</p> <p>Inhalation exposure from jasmine oil and lilial was not quantified as the product is expected to be used outside. Exposure by the inhalation route is therefore expected to be minimal.</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p>

Exposure scenario	Assumptions
Face makeup liquid (lilial)	<p>Concentration: 1% lilial</p> <p>Product amount: 0.54 g (adult) (Loretz et al. 2016); 0.41 g (14–18 yrs) (Ficheux et al. 2016); 0.39 g (9–13 yrs) (SA adjustment); 0.34 g (SA adjustment) Frequency: assumed minimum frequency of 1</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model. Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance. Exposure and emission duration: 20 h (adult); 24 h for all other subpopulations. Molecular weight matrix: 1000 g/mol Temperature: 32°C Room volume: 20 m³ Ventilation rate: 0.6/h Surface area: surface area of face, 585 cm² (adult); 370 cm² (14–18 yrs); 350 cm² (9–13 yrs); 305 cm² (4–8 yrs)</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
Nail polish (lilial)	<p>Concentration: 3% lilial</p> <p>Product amount: 0.16 g (adults, 14–18 yrs and 9–13 yrs); 0.06 g (4–8 yrs and 2–3 yrs) (Ficheux et al. 2014) Frequency: assumed minimum frequency of 1</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using ConsExpo exposure to vapour–evaporation–constant release area model.</p>

Exposure scenario	Assumptions
	<p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance.</p> <p>Exposure and emission duration: 5 min</p> <p>Molecular weight matrix: 124 g/mol</p> <p>Temperature: 32°C</p> <p>Room volume: 1 m³</p> <p>Ventilation rate: 1/h</p> <p>Mass transfer coefficient: 10 m/h</p> <p>Release area: 0.0019 m²</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
Nail polish remover (lilial)	<p>Concentration: 0.1% lilial</p> <p>Product amount: 2.25 g (adults, 14–18 yrs and 9–13 yrs); 0.76 g (4–8 yrs and 2–3 yrs) (Ficheux et al. 2014)</p> <p>Frequency: assumed minimum frequency of 1</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p> <p>Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance.</p> <p>Exposure and emission duration: 5 min</p> <p>Molecular weight matrix: 75 g/mol</p> <p>Temperature: 32°C</p> <p>Room volume: 1 m³</p> <p>Ventilation rate: 1/h</p> <p>Mass transfer coefficient: 10 m/h</p> <p>Release area: 0.0025 m²</p>

Exposure scenario	Assumptions
	<p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
<p>Sunless tanning products for the face (lotion) (lilial)</p>	<p>Concentration: 1% lilial Product amount: 1.5 g (adults and 1–18 yrs) (Ficheux et al. 2016) Frequency: assumed minimum frequency of 1</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model. Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance. Exposure and emission duration: 24 h Molecular weight matrix: 1000 g/mol Temperature: 32°C Room volume: 58 m³ Ventilation rate: 0.5/h Surface area: surface area of half head, 585 cm² (adults); 370 cm² (14–18 yrs)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p>
<p>Air freshener (solid gel) (lilial)</p>	<p>Concentration: 5% lilial (SDS 2016)</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–instantaneous release model. Product amount: 1.5 g/day (based on a product size of approximately 45 g and 30 days of use) Exposure duration: 24 h</p>

Exposure scenario	Assumptions
	<p>Room volume: 20 m³ Ventilation rate: 0.6/h</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p>
Air freshener (liquid plug-in) (subgroup 2)	<p>Concentration: lilial 3% (SDS 2017a), 1% myrac-aldehyde (SDS 2020)</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–constant rate model.</p> <p>Product amount: 0.5 g/day (based on a product size of approximately 26 g and 50 days of use, assuming a density of 1 g/mL) Frequency : 7.3/year (50 days/365 days) Exposure duration and emission duration: 50 days (RIVM 2021b) Room volume: 20 m³ (RIVM 2021b) Ventilation rate: 0.6/h (RIVM 2021b)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p>

Table A-2. Parameters for estimating dermal, inhalation, and incidental oral exposures to cleaning products

Exposure scenario	Assumptions
Mixing, loading, and application of an all-purpose floor cleaner (liquid) (adult) (jasmine oil, lilial)	<p>Concentration: 1% jasmine oil (ACI 2018), 1% lilial</p> <p>Mixing and loading (dermal) Product amount: 0.01 g</p> <p>Application (dermal) Product amount: 0.36 g {16.4 g/L concentration of product in cleaning solution * 21.85 mL [based on film thickness approach of 0.01 cm * exposed surface area of 2185 cm² for hands (910 cm²) and forearms (½ arms 2550 cm²)], 1 mL = cm³}</p> <p>Total dermal exposure: Dermal mixing and loading + Dermal application</p>

	<p>Mix/load (inhalation) Inhalation–exposure to vapour–evaporation–constant release area: Exposure duration: 0.75 min Product amount: 500 g Room volume: 1 m³ Ventilation rate: 0.5/h Release area: 20 cm² Emission duration: 0.3 min Application temperature: 20°C Molecular weight matrix: 36 g/mol</p> <p>Application (inhalation) Inhalation–exposure to vapour–evaporation–increasing release: Exposure duration: 240 min Amount of solution used: 900 g Dilution: 62 times Room volume: 58 m³ Ventilation rate: 0.5/h Release area: 22 m² Application duration: 20 min Temperature: 20°C Molecular weight matrix: 18 g/mol</p> <p>Air concentration (time-weighted average) = {[mean event concentration (mix/load) (mg/m³) * 0.75 min] + [mean event concentration (application) (mg/m³) * 240 min]} ÷ [total time 240.75 min / (24 h * 60 min)]</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Total dermal exposure (mg/kg bw/day) + Total inhalation exposure (mg/kg bw/day)</p>
<p>Exposure from contacting cleaned floors (toddler) (jasmine oil, lilial)</p>	<p>Concentration: 1% jasmine oil (ACI 2018), 1% lilial</p> <p>Calculations are based on the US EPA Residential SOPs (2012b), Section 7.</p> <p>Dermal Calculated using the following algorithm: Exposure (mg/kg bw/day) = [deposited residue (mg/cm²) * fraction available for transfer (%) * transfer coefficient (cm²/h) * exposure time (h) * dermal absorption (%)]/body weight</p>

	<p>Deposited residue (mg/cm²): calculated assuming 14 g of product per 22 m² of floor (ConsExpo Cleaning Fact Sheet RIVM 2018) * 1 000 mg/g * 1 m²/10 000 cm²</p> <p>Transfer coefficient: 1 927 cm²/h [adult transfer coefficient (6 800 cm²/h) adjusted for the body surface area of a 1–2 year old (0.28, that is, 5 300 cm²/18 700 cm²)] (Health Canada 2019b).</p> <p>Fraction available for transfer: 8%</p> <p>Exposure time: 2 h; exposure time for hard surfaces represents time spent in kitchens and bathrooms</p> <p>Incidental oral (that is, hand-to-mouth exposure) Calculated using the following algorithm: Exposure (mg/day) = [HR (mg/cm²) * (F_M * SA_H (cm²)) * (ET * N_Replen) * (1 – (1 – SE)^{Freq_HtM/N_Replen})]</p> <p>HR: hand residue loading (mg/cm²); calculated using the following algorithm: HR = [F_{aihands} * Dermal exposure (mg) (calculated above)] / (SA_H * 2)</p> <p>F_{aihands}: 0.15 (unitless); fraction of active ingredient on hands compared to total surface residue from jazzercise study SA_H: 150 cm²; typical surface area of one hand</p> <p>F_M: 0.13 (unitless); fraction of hand mouthed per event SA_H: 150 cm²; typical surface area of one hand ET: 2 h; 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</p> <p>Combined exposure = Dermal + inhalation+ Incidental oral</p>
<p>Mixing, loading, and application of an all-purpose cleaner (aerosol) (adult) (jasmine oil)</p>	<p>Concentration: 1% jasmine oil (ACI 2018)</p> <p>Inhalation-exposure to spray-spraying</p> <p>Spray duration: 0.23 min</p> <p>Exposure duration: 60 min</p> <p>Room volume: 15 m³</p> <p>Room height: 2.5 m</p> <p>Ventilation rate: 2.5/h</p> <p>Mass generation rate: 1.6 g/s</p> <p>Airborne fraction: 0.006</p> <p>Density non-volatile: 1 g/cm³</p>

	<p>Initial particle distribution: lognormal Median (CV): 2.4 µm (0.37) Inhalation cut-off diameter: 15 µm</p> <p>Inhalation during leave-on and wiping is expected to be minimal due to the low vapour pressure of jasmine oil.</p> <p>Application (dermal) Product amount: 21.5 mg (46 mg/min * 28 s * 1 min/60 s)</p> <p>Wiping (dermal) Product amount: 318.5 mg (0.14 g/mL concentration of product on surface * 2. mL {based on film thickness approach of 0.01 cm * exposed surface area of 227.5 cm² for inside surface of one hand [¼ surface area of hands (910 cm²)]}, 1 mL = cm³) * 1000 mg/g</p> <p>Total combined exposure: Inhalation application + Dermal application + Dermal wiping</p>
<p>Mixing and loading a liquid laundry detergent for hand-washing, and hanging hand-washed clothes (adult) (lilial)</p>	<p>Concentration: 1% lilial</p> <p>Mixing and loading (dermal) Product amount: 530 mg (pouring via cap)</p> <p>Washing (dermal) Product amount: 192.28 mg [calculated using a film-thickness approach, 8.8 mg/mL (concentration of regular liquid in washing water) * 2185 cm² (surface area of forearms and hands) * 0.01 cm]</p> <p>Hanging (dermal): 80.08 mg [calculated using a film-thickness approach, 8.8 mg/mL (concentration of regular liquid in washing water) * 910 cm² (surface area of hands) * 0.01 cm]</p> <p>Total dermal exposure (mg/kg bw/day) = [Dermal (mixing/loading) (mg) + Dermal (washing) (mg) + Dermal (hanging) (mg)] * dermal absorption/Body weight</p> <p>Mixing and loading (inhalation) Inhalation–exposure to vapour–evaporation–constant release area: Exposure duration: 0.75 min Product amount: 500 g Room volume: 1 m³ Ventilation rate: 0.6/h Release area: 20 cm² Emission duration: 0.3 min</p>

	<p>Application temperature: 20°C Mass transfer coefficient: 90 g/mol</p> <p>Washing (inhalation) Inhalation–exposure to vapour–evaporation–constant Exposure duration: 10 min Amount of solution used: 15 kg Dilution: 110 (regular liquid) Room volume: 20 m³ Ventilation rate: 0.6/h Release rate: 1500 cm² Emission duration: 10 min Application temperature: 40°C Molecular weight matrix: 18 g/mol</p> <p>Hanging (inhalation) Exposure duration: 240 min Amount of solution used: 5 kg Dilution: 110 (regular liquid) Room volume: 20 m³ Ventilation rate: 0.6/h Release area: 10 m² Application duration: 17 min Application temperature: 20°C Molecular weight matrix: 18 g/mol</p> <p>Air concentration (24 h TWA) = {[mean air concentration – mixing and loading (mg/m³) * time (0.75 min)] + [mean air concentration – washing (mg/m³) * time (10 min)] + [mean air concentration – hanging (mg/m³) * time (240 min)]} / {[total time (250.75 min)] * [250.75 min * (24 hrs/60 min)]}</p> <p>Inhalation exposure (mg/kg bw/day) = [24 h TWA air concentration (mg/m³) * daily inhalation rate (m³/day)]/Body weight (kg)</p> <p>Total combined exposure (mg/kg bw/day) = total dermal exposure (mg/kg bw/day) + total inhalation exposure (mg/kg bw/day)</p>
<p>Mixing and loading a liquid for machine washing, hanging machine-washed clothes, and migration from</p>	<p>Concentration: 5% jasmine oil (ACI 2018)</p> <p>Mixing and loading (dermal) Product amount: 530 mg (pouring via cap)</p> <p>Hanging laundry (dermal)</p>

<p>washed clothes (adult) (jasmine oil)</p>	<p>Product amount: 7 mg [0.77 g/L (concentration of detergent in the water sorbed by the textile) * 9.1 mL (based on film thickness approach of 0.01 cm * exposed surface area of 910 cm² for both hands, 1 mL = cm³) * 1 L/1000 mL * 1000 mg/g]</p> <p>Mixing and loading (inhalation) Inhalation–exposure to vapour–evaporation–constant release area: Exposure duration: 0.75 min Product amount: 500 g Room volume: 1 m³ Ventilation rate: 0.6/h Release area: 20 cm² Emission duration: 0.3 min Application temperature: 20°C Mass transfer coefficient: 90 g/mol</p> <p>Hanging (inhalation) Inhalation–exposure to vapour–evaporation–increasing release area mode; Exposure duration: 240 min Amount of solution used: 5000 g Dilution: 1300 (regular liquid) Room volume: 20 m³ Ventilation rate: 0.6/h Release area: 10 m² Application duration: 10 min Application temperature: 20°C Molecular weight matrix: 18 g/mol</p> <p>Air concentration (24 h TWA) = {[mean air concentration – mixing and loading (mg/m³) * time (0.75 min)] + [mean air concentration – hanging (mg/m³) * time (240 min)]} / {[total time (250.75 min)] * [250.75 min * (24 h/60 min)]}</p> <p>Inhalation exposure (mg/kg bw/day) = (24 h TWA air concentration (mg/m³) * daily inhalation rate (m³/day)/Body weight (kg)</p> <p>Migration from machine-washed clothes (dermal) Algorithm is based on the US EPA Residential SOPs (2012b), Section 9 (Impregnated Materials)</p>
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	<p>Dermal exposure (mg) = concentration (5%) * surface residue concentration (mg/cm²) [weight fraction of product on textile * material weight-surface area density (mg/cm²)] * surface area (cm²) * fraction of body exposed to clothing * material to skin transfer efficiency * dermal absorption</p> <p>Weight fraction of product on textile: 7.6 x 10⁻⁴ (regular liquid) (RIVM 2018) Material weight-surface area density: 24 mg/cm² (heavy cotton/synthetic mix) (US EPA 2012) Surface area (cm²): total surface area minus the head and hands (RIVM 2018) Fraction of body exposed to clothing: 0.8 (RIVM 2018) Material to skin transfer efficiency: 0.06 (US EPA 2012)</p> <p>Total dermal exposure = Dermal mixing and loading + Dermal hanging washed clothing + Dermal migration from clothes</p> <p>Total combined exposure (mg/kg bw/day) = total dermal exposure (mg/kg bw/day) + total inhalation exposure (mg/kg bw/day)</p>
<p>Migration from washed clothes (all subpopulations except adults) (see above) (jasmine oil)</p>	<p>Concentration: 5% jasmine oil (ACI 2018)</p> <p>Migration from machine-washed clothes (dermal): Algorithm is based on the US EPA Residential SOPs (2012), Section 9 (Impregnated Materials) Dermal exposure (mg) = concentration (5%) * surface residue concentration (mg/cm²) [weight fraction of product on textile * material weight-surface area density (mg/cm²)] * surface area (cm²) * fraction body exposed to clothing * material to skin transfer efficiency * dermal absorption</p> <p>Weight fraction of product on textile: 7.6 x 10⁻⁴ (regular liquid) (RIVM 2018) Material weight-surface area density: 24 mg/cm² (heavy cotton/synthetic mix) (US EPA 2012) Surface area (cm²): total surface area minus the head and hands (RIVM 2018) Fraction of body exposed to clothing: 0.8 (RIVM 2018) Material to skin transfer efficiency: 0.06 (US EPA 2012)</p> <p>Incidental oral (mouthing of washed textiles) (1–2 yrs only) Algorithm from US EPA ADD for Treated Textiles Incidental oral exposure (mg) = concentration (5%) * surface residue (mg/cm²) * surface area mouthed (cm²) * saliva extraction factor</p>

	<p>Surface residue (mg/cm²): see calculation above Surface area mouthed (cm²): 10 cm² Saliva extraction factor: 0.48</p> <p>Combined exposure (1–2 yrs only) = Dermal migration from washed clothing + Incidental oral from mouthing washed clothing or textiles</p>
Toilet bowl cleaner (adult) (lilial)	<p>Concentration: 1% lilial</p> <p>Application (dermal) Product amount: 386 mg [contact rate (193 mg/min) * release duration (2 min)]</p> <p>Dermal exposure (mg/kg bw/day) = [product amount (mg) * dermal absorption]/body weight</p> <p>Application (inhalation) Inhalation–exposure to vapour–evaporation–constant release model Exposure duration: 7 min Product amount: 80 g (bleach toilet) Room volume: 2.5 m³ Ventilation rate: 2/h Release area: 0.175 m² Emission duration: 2 min Application temperature: 20°C Molecular weight matrix: 21 g/mol</p> <p>Inhalation exposure (mg/kg bw/day): [daily air concentration (mg/m³) * daily inhalation rate (m³/day)]/body weight</p> <p>Combined exposure (mg/kg bw/day) = dermal exposure (mg/kg bw/day) + inhalation exposure (mg/kg bw/day)</p>
Carpet deodorizer (adult) (lilial)	<p>Concentration: 1% lilial</p> <p>Assessed as a carpet cleaner</p> <p>Application (dermal) Product amount: 30.8 mg [contact rate (2.8 mg/min) * release duration (11 min)]</p> <p>Dermal exposure (mg/kg bw/day) = [product amount (mg) * dermal absorption]/body weight</p> <p>Inhalation</p>

	<p>Inhalation–exposure to vapour–evaporation–increasing release area model Exposure duration: 30 min Product amount: 2200 g Room volume: 58 m³ Ventilation rate: 0.5/h Application duration: 11 min Application temperature: 20°C Molecular weight matrix: 45 g/mol Release area: 22 m²</p> <p>Inhalation exposure (mg/kg bw/day) = [daily air concentration (mg/m³) * daily inhalation rate (m³/day)]/body weight</p> <p>Combined exposure (mg/kg bw/day) = dermal exposure (mg/kg bw/day) + inhalation exposure (mg/kg bw/day)</p>
<p>Exposure from contacting cleaned carpets (carpet deodorizer) (toddler) (lilial)</p>	<p>Concentration: 1% lilial</p> <p>Calculations are based on the US EPA Residential SOPs (2012), Section 7.</p> <p>Dermal Calculated using the following algorithm: Exposure (mg/kg bw/day) = [deposited residue (mg/cm²) * fraction available for transfer (%) * transfer coefficient (cm²/hr) * exposure time (hrs) * dermal absorption (%)]/body weight</p> <p>Deposited residue (mg/cm²): calculated assuming 2 200 g of product per 22 m² of floor * 10% to account for vacuuming (ConsExpo Cleaning Fact Sheet, RIVM 2018) * 1 000 mg/g * 1 m²/10 000 cm²</p> <p>Transfer coefficient: 1 927 cm²/hr (adult transfer coefficient [6 800 cm²/h] adjusted for the body surface area of a 1–2 year old [0.28, that is, 5 300 cm²/18 700 cm²]) (Health Canada 2019b).</p> <p>Fraction available for transfer: 6% Exposure time: 4 h; exposure time for carpets</p> <p>Incidental oral (that is, hand-to-mouth exposure) Calculated using the following algorithm: Exposure (mg/day) = [HR (mg/cm²) * (F_M * SA_H (cm²)) * (ET * N_Replen) * (1 - (1 - SE)^{Freq_HtM/N_Replen})]</p> <p>HR: hand residue loading (mg/cm²); calculated using the following algorithm:</p>

	<p>HR = $[F_{ai_{hands}} * \text{Dermal exposure (mg) (calculated above)}] / (SA_H * 2)$</p> <p>$F_{ai_{hands}}$: 0.15 (unitless); fraction of active ingredient on hands compared to total surface residue from jazzercise study SA_H: 150 cm²; typical surface area of one hand</p> <p>F_M: 0.13 (unitless); fraction of hand mouthed per event SA_H: 150 cm²; typical surface area of one hand ET: 4 h; 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</p> <p>Combined exposure (mg/kg bw/day) = Dermal + Incidental oral + inhalation (calculated using the daily air concentration from application)</p>
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Appendix B. Parameters for estimating dermal and inhalation exposures to Do-It-Yourself products

Table B-1. Parameters for estimating dermal and inhalation exposures to DIY products available to consumers

Exposure scenario	Assumptions
DIY aromatic diffuser (violet oil, bay oil, tarragon oil, jasmine oil)	<p>Concentration: 100% violet oil, 100% bay oil, 100% tarragon oil, 100% jasmine oil</p> <p>Product amount for the dermal exposure is based on approximately 2 drops of essential oil (professional judgment) being added to the stationary device (1 drop is equivalent to 0.05 mL)* the oil density</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption] ÷ Body weight</p> <p>Air concentrations were modelled using an evaporation–constant rate model (RIVM 2021b). Product amount: 0.92 g Exposure duration: 10 h Room volume: 20 m³ Ventilation rate: 0.6/h Emission duration: 10 h</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day) * Frequency (365 times/365 (year))] ÷ Body weight</p> <p>For bay oil and tarragon oil, LADDs were also calculated using the following formula (HC 2013): LADD (mg/kg bw/day) = ((exposure (mg/kg bw/day) 0–5 mths * time in lifestage (0.5 yr)) + (exposure (mg/kg bw/day) 6–12 mths * time in lifestage (0.5 yr)) + (exposure (mg/kg bw/day) 1 yr * time in lifestage (1 yr)) + (exposure (mg/kg bw/day) 2–3 yrs * time in lifestage (2 yrs)) + (exposure (mg/kg bw/day) 4–8 yrs * time in lifestage (5 yrs)) + (exposure (mg/kg bw/day) 9–13 yrs * time in lifestage (5 yrs)) + (exposure (mg/kg bw/day) 14–18 yrs * time in lifestage (5 yrs)) + (exposure (mg/kg bw/day) adult (19+) * time in lifestage (59 yrs)) / Average lifetime (78 yrs)</p>

Exposure scenario	Assumptions
DIY massage oil (bay oil, tarragon oil, jasmine oil)	<p>Concentration: 3% bay oil, 3% tarragon oil, 3% jasmine oil</p> <p>Product amount: 3.2 g (adults); 2.9 g (14–18 yrs); 2.3 g (9–13 yrs); 1.9 g (4–8 yrs); 1.8 g (2–3 yrs, 1 yr, 6–11 mths, 0–5 mths) (Ficheux et al. 2016)</p> <p>Frequency: jasmine oil, 1 for all subpopulations. Bay and tarragon oil, for calculation of LADDs, a frequency of 0.11/day (adults and 14–18 yrs) and 0.13/day (all other subpopulations) (Ficheux et al. 2015)</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model. Product amount: as above, adjusted to account for the amount remaining on the skin surface following dermal absorption of the substance.</p> <p>Exposure and emission duration: 8.5 h (except 0–5 months: 8.25 h)</p> <p>Molecular weight matrix: 3000 g/mol</p> <p>Temperature: 32°C</p> <p>Room volume: 16 m³</p> <p>Ventilation rate: 0.6/h</p> <p>Surface area: equivalent to total surface area minus half head and half truck for adults, 14–18 yrs and 9–13 yrs, and total surface area minus half head for all other subpopulations. 14 670 cm² (adults); 13 385 cm² (14–18 yrs); 10 395 cm² (9–13 yrs); 8 595 cm² (4–8 yrs); 6 225 cm² (2–3 yrs); 4 865 cm² (1 yr); 4 090 cm² (6–11 mths); 3 180 cm² (0–5 mths)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day) * Frequency (as above, for LADD calculation only)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p> <p>For bay oil and tarragon oil, LADDs were also calculated using the following formula (HC 2013):</p>

Exposure scenario	Assumptions
	<p>LADD (mg/kg bw/day) = ((combined exposure (mg/kg bw/day) 0–5 mths * time in lifestage (0.5 yr)) + (combined exposure (mg/kg bw/day) 6–12 mths * time in lifestage (0.5 yr)) + (combined exposure (mg/kg bw/day) 1 yr * time in lifestage (1 yr)) + (combined exposure (mg/kg bw/day) 2–3 yrs * time in lifestage (2 yrs)) + (combined exposure (mg/kg bw/day) 4–8 yrs * time in lifestage (5 yrs)) + (combined exposure (mg/kg bw/day) 9–13 yrs * time in lifestage (5 yrs)) + (combined exposure (mg/kg bw/day) 14–18 yrs * time in lifestage (5 yrs)) + (combined exposure (mg/kg bw/day) adult (19+) * time in lifestage (59 yrs)))/Average lifetime (78 yrs)</p>
<p>DIY bath oil product (violet oil, bay oil, tarragon oil, jasmine oil)</p>	<p>Concentration: 100% violet oil, 100% bay oil, 100% tarragon oil, 100% jasmine oil</p> <p>Product amount is based on approximately 10 drops of pure essential oil being added to a bath filled with 120 L water (1 drop is equivalent to 0.05 mL), multiplied by the oil density (RIVM 2006).</p> <p>Dermal product amount was calculated using a film-thickness approach where the volume of water that comes into contact with skin is equal to the surface area of the entire body, except the head, multiplied by the layer thickness of liquid film on the skin (0.01 cm; ECHA 2015). Therefore, for adults, product amount = (10 drops * 0.05 mL * oil density) / 120 L * 1 000 mg/g * 0.1753 L (0.01 cm * 17 530 cm² = 175.3 cm³ or mL = 0.1753 L) (16 460 cm² surface area 14–18 yrs and 12 700 cm² surface area for 9–13 yrs).</p> <p>Frequency: 0.29 (all subpopulations) (calculation of LADD only) (Bremmer et al. 2006)</p> <p>Frequency: 1 (all subpopulations)</p> <p>For bay oil, tarragon oil, and jasmine oil, dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product (g/application) * mean daily frequency * product concentration * dermal absorption * retention factor * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model.</p>

Exposure scenario	Assumptions
	<p>Inhalation product amount: (10 drops * 0.05 mL * oil density) – dermal product amount (to account for the amount systemically absorbed by the dermal route) Exposure and emission duration: 45 min Molecular weight matrix: 18 g/mol Temperature: 32°C Room volume: 10 m³ Ventilation rate: 2/h Surface area: 11 552 cm² (equivalent to the surface area of a bathtub, standard tub dimensions of 76 cm x 152 cm)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day) * Frequency (calculation of LADD only)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p> <p>For bay oil and tarragon oil, a LADD was also calculated using the following formula (HC 2013):</p> <p>LADD (mg/kg bw/day) = {[combined exposure (mg/kg bw/day) 9–13 yrs * time in lifestage (5 yrs)] + [combined exposure (mg/kg bw/day) 14–18 yrs * time in lifestage (5 yrs)] + [combined exposure (mg/kg bw/day) adult (19+) * time in lifestage (59 yrs)]}/Average lifetime (78 yrs)</p>
<p>DIY body moisturizer (violet oil, bay oil, tarragon oil, jasmine oil)</p>	<p>Concentration: 3% violet oil, 3% bay oil (assuming the 0.002% maximum concentration of methyl eugenol permitted according to the cosmetics hotlist), 3% tarragon oil, 3% jasmine oil</p> <p>Product amount: 10 g (adults and 14–18 yrs); 7.7 g (9–13 yrs); 5 g (4–8 yrs); 4.1 g (2–3 yrs); 3.1 g (1 yr); 2.5 g (6–11 mths); 2 g (0–5 mths) (Ficheux et al. 2016) Frequency: 1 (adults) (Wu et al. 2010; Ficheux et al. 2015). For all other subpopulations, the mean frequency was assumed to be 1. For bay oil and tarragon oil (calculation of LADD), a frequency of 0.8/day was used for all other subpopulations (Wu et al. 2010; Ficheux et al. 2015).</p> <p>For bay oil, tarragon oil, and jasmine oil, dermal exposure (mg/kg bw/day) was calculated using the following formula:</p>

Exposure scenario	Assumptions
	<p>[mean product (g/application) * mean daily frequency * product concentration * dermal absorption * conversion factor (1000 mg/g)] ÷ Body weight</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–evaporation–constant release area model. Product amount: adjusted for unclothed surface area of short-sleeved shirt and shorts. 4.87 g (adults); 4.65 g (14–18 yrs); 3.61 g (9–13 yrs); 2.3 g (4–8 yrs); 1.85 g (2–3 yrs); 1.45 g (1 yr); 1.16 g (0–5 mths); 0.93 g (0–5 mths). Exposure and emission duration: 24 h Molecular weight matrix: 1000 g/mol Temperature: 32°C Room volume: 58 m³ Ventilation rate: 0.5/h Surface area: equivalent to arms, ¾ legs, hands, and ½ feet (short-sleeved shirt and shorts); 8543 cm² (adults); 7655 cm² (14–18 yrs); 5953 cm² (9–13 yrs); 3813 cm² (4–8 yrs); 2685 cm² (2–3 yrs); 2070 cm² (1 yr); 1703 cm² (6–11 mths); 1325 cm² (0–5 mths)</p> <p>Inhalation exposure (mg/kg bw/day) = [Air concentration (mg/m³) (24 h time-weighted average) * Inhalation rate (m³/day) * Frequency (calculation of LADD only)] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p> <p>For bay oil and tarragon oil, LADD was also calculated using the following formula (HC 2013):</p> <p>LADD (mg/kg bw/day) = {[combined exposure (mg/kg bw/day) 0–5 mths * time in lifestage (0.5 yr)] + [combined exposure (mg/kg bw/day) 6–12 mths * time in lifestage (0.5 yr)] + [combined exposure (mg/kg bw/day) 1 yr * time in lifestage (1 yr)] + [combined exposure (mg/kg bw/day) 2–3 yrs * time in lifestage (2 yrs)] + [combined exposure (mg/kg bw/day) 4–8 yrs * time in lifestage (5 yrs)] + [combined exposure (mg/kg bw/day) 9–13 yrs * time in lifestage (5 yrs)] + [combined exposure (mg/kg bw/day) 14–18 yrs * time in lifestage (5 yrs)] + [combined exposure (mg/kg bw/day) adult (19+) * time in lifestage (59 yrs)]}/Average lifetime (78 yrs)</p>
DIY facial steamer	Concentration: 100% violet oil, 100% jasmine oil

Exposure scenario	Assumptions
(violet oil, jasmine oil)	<p>Product amount is based on approximately 10 drops of essential oil being added to the stationary device (1 drop is equivalent to 0.05 mL) * density (RIVM 2006; HC 2015).</p> <p>Frequency: assumed to be 1 (adults, 14–18 yrs, 9–13 yrs, 4–8 yrs)</p> <p>Air concentrations were modelled using the ConsExpo exposure to vapour–constant rate model. Product amount: as cited above Exposure and emission duration: 20 min Room volume: 1 m³ Ventilation rate: 0.5/h (professional judgment)</p> <p>It is assumed that 50% of the mean event concentration will be inhaled and 50% of the mean event concentration will be exposed dermally. For inhalation exposure, after 20 minutes of facial steaming, it is assumed that a person remains in a 20 m³ room for 3 hours and 40 minutes. It is assumed that a 1-year-old bystander is present in the room for 4 hours.</p> <p>Inhalation exposure for 20 min (mg/kg bw/day) = {Mean event concentration (mg/m³) * 0.5 * [Inhalation rate (m³/day) * exposure time (20 min) ÷ (60*24)]* room volume} ÷ Body weight</p> <p>Dermal product amount: mean event concentration (mg/m³) * room volume (1 m³) * 0.5</p> <p>Dermal exposure (mg/kg bw/day) was calculated using the following formula: [mean product amount in air (mg/application) * mean daily frequency * dermal absorption] ÷ Body weight</p> <p>Combined exposure (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) + Inhalation exposure (mg/kg bw/day)</p> <p>Secondary inhalation exposure for 3 hours and 40 minutes:</p> <p>Total amount inhaled in 20 min (mg) = mean event concentration (mg/m³) * 0.5 * air inhaled in 20 min (m³) Product amount in air after 20 min (mg) = [mean event concentration (mg/m³) * 0.5 * room volume (1 m³)] – total amount inhaled in 20 min (mg)</p>

Exposure scenario	Assumptions
	<p>Product amount in air after 20 min spread in the 20 m³ room (mg/m³) = Product amount in air after 20 min (mg) ÷ 20 m³</p> <p>Amount inhaled in 3 h and 40 min (mg/day) = Product amount in air after 20 min spread in the 20 m³ room (mg/m³) * inhalation rate (m³/day) * [220 min ÷ (60 min/h * 24 h/day)]</p> <p>Inhalation exposure for the remainder of 3 h and 40 min (mg/kg bw/day) = Amount inhaled in 3 h and 40 min (mg/day) ÷ Body weight</p> <p>Inhalation exposure (mg/kg bw/day) for bystanders (1-year-old only) = Product amount in air after 20 min spread in the 20 m³ room (mg/m³) * Inhalation rate (m³/day) * [220 min ÷ (60 min/h * 24 h/day)] ÷ Body weight</p>