Government of Canada / Gouvernement du Canada

# Screening Assessment for the Challenge

# 1-Naphthalenepropanol, α-ethenyldecahydro-2-hydroxy-α,2,5,5,8α-pentamethyl-, [1R-[1α(R*),2β,4αβ,8αα]]-

# (Sclareol)

## Chemical Abstracts Service Registry Number

## 515-03-7

## Environment and Climate Change Canada

## Health Canada

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# Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment of 1-naphthalenepropanol, α-ethenyldecahydro-2-hydroxy-α,2,5,5,8α-pentamethyl-, [1R-[1α(R*),2β,4αβ,8αα]]- , hereinafter referred to as sclareol. The Chemical Abstracts Service Registry Number (CAS RN[1]) for sclareol is 515-03-7. Sclareol was identified as a priority for assessment as it met the categorization criteria under subsection 73(1) of CEPA.

Sclareol is naturally produced as a component in the essential oil of several genera (e.g., *Salvia* and *Stachys*) in the mint family, Lamiaceae. The essential oil containing sclareol may be produced by plants to protect themselves from pathogens (i.e., bacteria and/or fungi), foraging herbivores and/or influence the growth of neighbouring plants. Sclareol has been isolated in various plant species, such as *Salvia sclarea*, *Salvia officinalis*, *Salvia judaica, Salvia palaestina*, *Juniperus phoenicea*, *Cistus creticus*, and *Astragalus brachystachys*, including some 25 tobacco species, such as *Nicotiana glutinosa*, *Nicotiana tabacum*.

In Canada, sclareol is not reported to be imported or manufactured above the 100 kg reporting threshold or used above the 1000 kg threshold by any single company for the reporting years 2005 and 2006. However, a total estimated quantity of 76 to 1350 kg sclareol is currently used in Canada per year. Sclareol is a component of the clary sage essential oil, which was reported to be present in cosmetics, flavouring agents, aromatherapy products, and fragrances in Canada.

It is expected that sclareol, when produced by plants, will likely be degraded by soil bacteria or other fungal species, as a number of studies have shown that soil micro-organisms are capable of metabolizing sclareol. However, when the essential oil containing sclareol is extracted from these plants and incorporated into cosmetics, down-the-drain releases are likely to occur via wastewater treatment system effluent into the aquatic environment, where degradation is expected to occur much more slowly.

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Sclareol has low water solubility and has a tendency to partition to sediments if released to surface waters. On the basis of its physical and chemical properties, modelled data and a limited amount of experimental data, sclareol is expected to persist in water and sediment. Modelled data relating to its partitioning between octanol and water indicate that sclareol has a high potential to accumulate in the lipid tissues of organisms (bioconcentration factor [BCF]and bioaccumulation [BAF] factor values range from 4247 to 31 890). Modelled toxicity data for sclareol suggest that the substance can cause acute harm to aquatic organisms. Experimental microbial toxicity data also suggest that sclareol causes harm to bacteria and fungi.

Given the relatively small amounts of sclareol known to be in commerce in Canada and its uses, which can lead to disperse releases to the environment, ecological exposure to sclareol is expected to be low. Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from sclareol. It is concluded that sclareol does not meet the criteria under paragraph 64(*a*) or (*b*) of CEPA as it is 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 available information, exposure of the general population to sclareol is expected to be negligible given the low reports of use of sclareol in Canada in 2006. The general population is expected to be exposed predominantly via the dermal route from the presence of sclareol, a component of clary sage essential oil, in cosmetics. On the basis of the available information on health effects of sclareol, it was not considered to have high hazard potential. A comparison of conservative upper-bounding estimates of dermal exposure to sclareol from the presence of clary sage essential oil in cosmetics to a level at which no adverse effects were observed in experimental animals, resulted in margins of exposure that were considered adequate to address uncertainties in the health effects and exposure databases. On the basis of the available information, it is concluded that sclareol does not meet the criteria in paragraph 64(*c*) of CEPA, as it is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

On the basis of the information available, it is concluded that sclareol does not meet any of the criteria set out in section 64 of CEPA.

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# 1. Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or to human health.

On the basis of the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that:

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherent toxicity to aquatic organisms (iT), and were believed to be in commerce in Canada; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE) and had been identified as posing a high hazard to human health on the basis of classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006a), that challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment, and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as high priorities.

The substance, 1-naphthalenepropanol, α-ethenyldecahydro-2-hydroxy-α,2,5,5,8α-pentamethyl-, [1R-[1α(R*),2β,4αβ,8αα]]-, was identified as a priority for assessment as it met categorization criteria under subsection 73(1) of CEPA (ECCC, HC [modified 2007]). The “Challenge” for this substance was published in the *Canada Ga*zette on December 26, 2009 (Canada 2009a, 2009b). A substance profile was released at the same time. The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. No submissions of information pertaining to the properties, bioaccumulation potential, persistence, hazard, uses, or exposure of the substance were received under the Challenge.

Screening assessments focus on information critical to determining whether a substance meets the criteria as set out in section 64 of CEPA. Screening assessments

examine scientific information and develop conclusions by incorporating a weight-of-evidence approach and precaution.[1]

This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, and stakeholder research reports and from literature searches up to August 2010 for ecological and health sections of the screening assessment. In February 2017, a rapid search of the literature did not identify any significant new information that could influence the outcome of this assessment. Key studies were critically evaluated and modelling results may have been used to reach conclusions.

When available and relevant, information presented in hazard assessments from other jurisdictions was considered.

This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The ecological and human health portions of this assessment have undergone external written peer review/consultation. Approaches used in the screening assessments under the Challenge have been reviewed by an independent Challenge Advisory Panel. Additionally, the draft of this screening assessment was subject to a 60-day public comment period. No external comments were received on the draft screening assessment. The final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

The critical information and considerations upon which the screening assessment is based are summarized below.

[1] 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 undertaken under other sections of CEPA or other acts.

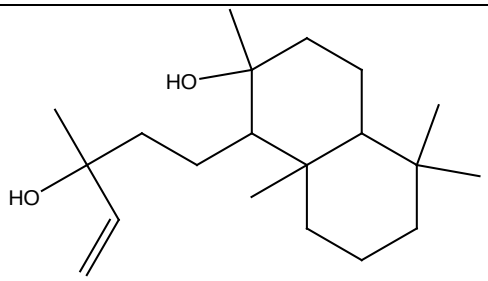
# 2. Substance identity

## 2.1 Substance name

For the purposes of this document, 1-naphthalenepropanol, α-ethenyldecahydro-2-hydroxy-α,2,5,5,8α-pentamethyl-, [1R-[1α(R*),2β,4αβ,8αα]]- will be referred to as sclareol, its common name.

**Table 2-1. Substance identity for sclareol**

| | |
|---|---|
| **Chemical Abstracts Service Registry Number (CAS RN)** | ***515-03-7*** |
| **DSL name[a]** | 1-Naphthalenepropanol, α-ethenyldecahydro-2-hydroxy-α,2,5,5,8α-pentamethyl-, [1R-[1α(R*),2β,4αβ,8αα]]- |
| **National Chemical Inventories (NCI) names[3b]** | 1-naphthalenepropanol, α-ethenyldecahydro-2-hydroxy-α,2,5,5,8α-pentamethyl-, (αR,1R,2R,4αS,8αS)- (TSCA, PICCS, ASIA-PAC, NZIoC)<br><br>1-naphthalenepropanol, α-ethenyldecahydro-2-hydroxy-α,2,5,5,8α-pentamethyl-, [1R-[1α(R*),2β,4αβ,8αα]]- (AICS)<br><br>[1R-[1α(R*),2β,4αβ,8αα]]-2-hydroxy-α,2,5,5,8α-pentamethyl-α-vinyldecahydronaphthalene-1-propan-1-ol (EINECS)<br><br>Sclareol (PICCS) |
| **Other names** | (-)-Sclareol;Labd-14-ene-8,13-diol; (13R)-{1R-[1α(R*),2β,4αβ,8αα]}-2-Hydroxy-α,2,5,5,8α-pentamethyl-α-vinyldecahydronaphtalene-1-propan-1-ol |
| **Chemical group (DSL stream)** | Discrete organics |
| **Major chemical class or use** | Bicyclic diterpenes |
| **Major chemical sub-class** | Labdane diterpene diols |
| **Chemical formula** | $C_{20}H_{36}O_2$ |
| **Chemical structure** | |

| | |
|---|---|
| |  |
| **SMILES**[c] | OC(C=C)(CCC(C(C(C(CC1)(C)C)CC2)(C1)C)C2(O)C)C |
| **Molecular mass** | 308.51 g/mol |

[a] Domestic Substances List.
[b] National Chemical Inventories (NCI). 2007: AICS (Australian Inventory of Chemical Substances); ASIA-PAC (Asia-Pacific Substances Lists); EINECS (European Inventory of Existing Commercial Chemical Substances); PICCS (Philippine Inventory of Chemicals and Chemical Substances); NZIoC (New Zealand Inventory of Chemicals); and TSCA (Toxic Substances Control Act Chemical Substance Inventory).
[c] Simplified molecular-input line entry system.

# 3. Physical and chemical properties

Table 3-1 contains experimental and modelled physical and chemical properties of sclareol that are relevant to its environmental fate. Sclareol is a white crystalline powder. The modelling program ACD/pKaDB (2005) predicts a primary acid dissociation constant (pKa1) of 15.5 and a secondary acid dissociation constant (pKa2) of 14.5. The substance ionizes little in water under environmentally relevant conditions and can therefore be evaluated using mass balance and quantitative structure-activity relationship (QSAR) models based on the properties of the neutral species.

QSAR models were used to generate data for some of the physical and chemical properties of sclareol. These models (except WSKOWWIN 2008) are based mainly on fragment addition methods, i.e., they rely on the structure of a chemical. Since these models only accept the neutral form of a chemical as input (in SMILES form), the modelled values shown in Table 3-1 are for the neutral form of sclareol.

**Table 3-1. Physical and chemical properties for sclareol**

| Property | Type | Value[a] | Descriptor | Reference |
|---|---|---|---|---|
| Melting point (ºC) | Experimental | 104-105 | NA | Jermstad 1927 |
| Melting point (ºC) | Experimental | 106[b] | NA | RIFM 1992 |
| Boiling point (ºC) | Experimental | 218–220[b] (at 19 mmHg) | NA | Sigma-Aldrich MSDS 2010 |
| Boiling point (ºC) | Experimental | > 340 | NA | RIFM 1992 |
| Density (g/cm$^3$) | Experimental | 0.954 | NA | Lookchem 2010 |
| Vapour pressure (Pa) | Experimental | < 0.1333[b] (< 0.001 mmHg) | 25 | RIFM 1992 |
| Vapour pressure (Pa) | Modelled | 0.3 (0.00212 mmHg) | NA | EPIsuite 2008 |

| Property | Type | Value[a] | Descriptor | Reference |
|---|---|---|---|---|
| Henry's law constant ($Pa \cdot m^3/mol$) | Modelled (Bond method) | 0.32 ($3.11 \times 10^{-6}$ $atm \cdot m^3/mole$) | NA | HENRYWIN 2008 |
| Henry's law constant ($Pa \cdot m^3/mol$) | Modelled (Group method) | Not calculable | NA | HENRYWIN 2008 |
| log $K_{ow}$ (octanol-water partition coefficient) (dimensionless) | Modelled | 6.0[b] | NA | KOWWIN 2008 |
| Log $K_{ow}$ (octanol-water partition coefficient) (dimensionless) | Modelled | 3.29 | NA | TOPKAT 2004 |
| Log $K_{ow}$ (octanol-water partition coefficient) (dimensionless) | Modelled | 4.93 | NA | ALOGPS c2001-2009 |
| Log $K_{oc}$ (organic carbon-water partition coefficient) (dimensionless) | Modelled | 3.1–3.4 | NA | KOCWIN 2008 |
| log $K_{oa}$ (octanol-air partition coefficient) (dimensionless) | Modelled | 9.9 | NA | KOAWIN 2008 |
| Water solubility (mg/L) | Modelled | 0.05[b] | 25 | WSKOWWIN 2008 |
| $pK_a$ (acid dissociation constant) (dimensionless) | Modelled | pKa1 = 15.5 pKa2 = 14.5 (acid form) | NA | ACD/$pK_a$DB 2005 |

[a] Values in parentheses represent the original ones as reported by the authors or as estimated by the models.
[b] Values selected in modelling with EPI Suite (2008).
NA = Not available.

# 4. Sources

Sclareol is naturally produced as a component in the essential oil of sage. This essential oil may be produced by the plant to protect itself from pathogens (i.e., bacteria and/or fungi), herbivores and/or influence the growth of neighbouring plants (Sirikanataramas et al. 2008). For example, the upper leaf surface of sage is covered with glandular hairs that secrete the essential oils that typically give the plant its distinct aroma. When the hairs are rubbed or brushed, some of the oil-bearing cells are ruptured, releasing the oil. This often results in the plant being unattractive to grazing animals and some insects.

*Salvia sclarea*, commonly known as clary sage, is the plant species most commonly used commercially for the extraction of sclareol. A biennial or perennial shrub with an aromatic smell (Pitarokili et al. 2002; Souleles and Argyriadou 1997; Tutin et al. 1972), *Salvia sclarea* was introduced into the United States and has been designated as a noxious weed by the US federal government and/or individual states as it is considered to pose a threat to forage production and plant biodiversity by displacing less competitive, more desirable species (NRCS 2010; NWCB 2008).

One of several genera commonly referred to as “sage,” *Salvia* is the largest genus of plants in the mint family (Lamiaceae), with approximately 700 to 900 species of shrubs, herbaceous perennials and annuals. Forty-eight species within the Lamiaceae family are considered naturalized in Canada, several of which (i.e., *Salvia sylvestris, Stachys arvenis*, *Stachys palustris*) have been designated as invasive species in Canada (CFIA 2008). *Salvia sylvestris* is listed as native to Ontario, introduced (i.e., as a result of human activity, either deliberate or accidental) in British Columbia, Alberta, and Manitoba, and extirpated (i.e., native but eradicated) in Saskatchewan (Brouillet et al. 2010). *Salvia sclarea* (found in Ontario) and *Salvia officinalis* (found in Ontario and Quebec) are listed as ephemerals (i.e., not established permanently, but recurring in the wild on a near-annual basis, usually from cultivation) (Brouillet et al. 2010). Of the 48 species in the Lamiaceae family considered naturalized in Canada, only *Salvia sclarea* and *Salvia officinalis* are currently known to produce sclareol in their essential oil.

In addition to *Salvia sclarea*, sclareol may also be found in *Salvia officinalis* (also known as “common sage” or Dalmatian sage) and its cultivars, *Salvia judaica* (Judean sage) (Boszomenyi et al. 2009), *Salvia palaestina* (Senatore et al. 2005), *Salvia poculata* (Kolak et al. 2009), *Salvia desoleana* (Soković et al. 2008), in some species of the genus *Stachys*, such as *S. ionica*, *S. sylvatica*, and *S. swainsonii* ssp. *scyronica* (Piozzi and Bruno 2009), in the essential oils of the leaves and berries of *Juniperus phoenicea* (El-Sawi et al. 2007), in the leaves of *Cistus creticus* (Demetzos et al. 1990) and in the plant *Astragalus brachystachys* (Choudhary et al. 2006). The leaves of some tobacco species, such as *Nicotiana glutinosa*, *Nicotiana tabacum* and 23 other *Nicotiana* species, also contain sclareol (Cutler et al. 1977; Kennedy et al. 1992).

The essential oils are extracted from plants by steam distillation or with organic solvents, typically for use as flavour or fragrance ingredients. The amount of sclareol in an essential oil extracted from a given plant varies depending on the section of the plant from which the essential oil is extracted (i.e., flower, leaves), the developmental stage of the plant (i.e., full blossom, at seed formation, full seed formation) (Farkas et al. 2005), the cultivation conditions (Peana et al. 1999), the country of origin (Schmiderer et al. 2008), and the extraction technique. Clary sage can be extracted for its essential oil or its "concrete." Concrete, in perfumery, is a semi-solid mass obtained by solvent extraction of fresh plant material. Essential oils are obtained by means of hydro-distillation of the plant material (Souleles and Argyriadou 1997), while the concrete is obtained by solvent extraction (Schmiderer et al. 2008; Lawrence 1986). Sclareol may be present at varying percentages (ranging from 0.06 to 20%) in the essential oil of various *Salvia* species, with higher percentages found in *Salvia palaestina* (~20%). While levels of sclareol can be more concentrated in concrete (> 70% in *Salvia sclarea*) (Senatore et al. 2005; Schmiderer et al. 2008; Esteban et al. 1996; Lawrence 1986), it is rarely used as fragrance in the cosmetic industry (Surburg and Panten 2006).

Historically, during the *Domestic Substances List* (DSL) nomination process (based on the years 1984 to 1986), the DSL use codes for "fragrance/perfume/deodorizer/flavouring agent" were identified for sclareol. The quantity reported was in the 1000 to 10 000 kg range (Environment Canada 1988), with fewer than four notifiers.

For the 2005 calendar year, no manufacture or import of sclareol above the 100 kg threshold, or use above the 1000 kg threshold, by any single company in Canada was reported in response to a CEPA section 71 survey notice (Canada 2006b; Environment Canada 2006). However, two companies identified themselves as having a stakeholder interest in the substance.

For the 2006 calendar year, no manufacture or import of sclareol above the 100 kg threshold or use above the 1000 kg threshold by any single company, was were reported in Canada in response to a CEPA section 71 survey notice (Canada 2009b; Environment Canada 2010). One company identified itself as a having a stakeholder interest in the substance.

Additional investigations (personal communications from the Canadian Federation of Aromatherapists and other associations, 2011; unreferenced) indicated that sclareol is currently used in Canada. Using a combination of reported information and conservative assumptions, lower and upper estimates of the quantity of sclareol in commerce were made. It is estimated that between 76 and 1350 kg of sclareol is used (see Table 4-1) in Canada per year. The total quantity of sclareol imported/used in Canada was estimated by summing the estimates of use in the fragrance, flavouring agents, cosmetics and aromatherapy industries. This may result in some double counting, as some aromatherapy products may be considered cosmetics and some fragrances may be used in the formulation of cosmetics. This information was taken into consideration for the assessment.

The following assumptions were used in calculating the quantity estimates in Canada:

- Companies involved in cosmetics, fragrances, and flavouring agents have indicated that the composition of clary sage essential oil is less than 5% sclareol. Therefore, the assumption is made that clary sage essential oil is composed of 5% sclareol when used in fragrances, cosmetics, and flavouring agents.
- For aromatherapy products, the low-end estimates are based on information reported by individual companies to their associations. For high-end estimates, it was assumed that the quantity provided by individual companies may also apply to other companies with similar activities.
- Products (e.g., fragrance) available in the United States may also be available to Canadians through industrial activities (i.e., import). Population market share assumptions between Canada and the United States were applied for low-end estimates. For high-end estimates, it was assumed that the quantity provided by individual companies may also apply to other companies with similar activities.
- Sclareol is an approved flavouring agent in the United States and elsewhere. It is assumed that food flavoured with sclareol is available in Canada. Population market share assumptions between Canada and the United States were utilized for low-end estimates. For high-end estimates, the quantities used in the United States were also applied in Canada.
- Neither clary sage essential oil nor sclareol are found in tobacco sold in Canada because of prohibitions on flavouring agent use in tobacco.

The commercial significance of clary sage essential oil or sclareol to industry, particularly companies involved in aromatherapy, is considered low to moderate. Many companies indicated low use quantities, low sales and the use of alternative substances (personal communications from Canadian Federation of Aromatherapists and other associations, 2011; unreferenced).

**Table 4-1. Total extrapolated quantity data for sclareol (CAS 515-03-7) per year**

| **Sector/product category** | **Total *(pure substance)* (kg)** | **Total *(pure substance or in clary sage essential oil)* (kg)** |
|---|---|---|
| Fragrances/Cosmetics | 14–159 | 62–507 |
| Flavour | 4–40 | 4–40 |
| Aromatherapy | NA | 10–802 |
| Tobacco | NA | NA |
| **Total** | **18–199** | **76–1350** |

NA = not available

# 5. Uses

In Canada, notification of fragrance components to Health Canada is not a requirement and sclareol, as such, was not identified in the Cosmetic Notification System (CNS). However, it is a component of the essential oil in *Salvia sclarea*, and approximately 800

cosmetic products containing this essential oil in concentrations varying between 0.1% and 30% were identified in the CNS (CNS 2010). Sclareol is not included on the List of Prohibited and Restricted Cosmetic Ingredients (more commonly referred to as the Cosmetic Ingredient Hotlist or simply the Hotlist), an administrative tool that Health Canada uses to communicate to manufacturers and others that certain substances, when present in a cosmetic, may contravene the general prohibition found in section 16 of the *Food and Drugs Act* or a provision of the *Cosmetic Regulations* (Health Canada 2011).

Clary sage essential oil is used as fragrance in insect repellents, insecticides, indoor flea and tick treatments for domestic animals, and carpet sanitizers (personal communication from the Pest Management Regulatory Agency, Health Canada, to Risk Management Bureau, Health Canada, dated November 2010; unreferenced). Sclareol is not listed as an approved food additive in the lists of permitted food additives under the *Food and Drugs Act* (Health Canada 2013).

The Flavor and Extract Manufacturers Association (FEMA) of the United States has listed sclareol as one of the 236 new flavouring ingredients generally recognized as safe (Smith et al. 2009). As sclareol is used as a food flavour in the United States and elsewhere (Smith et al. 2009; European Commission 2002; Ash and Ash 2003, 2006), it is possible that sclareol is used as a flavour in foods that are offered for sale in Canada. In Canada, food flavours are not regulated as food additives and are not required under the *Food and Drug Regulations* to undergo pre-market review. Flavouring ingredients can be added to any food that does not have a standard of identity and composition in the *Food and Drug Regulations* and to those foods that have a standard of identity and composition that allows for the addition of flavours to the food. Similarly, plant materials such as leaves, stems, and seeds containing sclareol may be added to foods without a regulatory standard and to foods having a standard where there is provision for the addition of spices or seasonings. Sclareol was not identified in food packaging applications or in formulations of incidental additives (personal communication from Food Directorate, Health Canada, to the Risk Management Bureau, Health Canada, dated August 2010; unreferenced).

Sclareol is not listed in the Drug Product Database, the Therapeutic Products Directorate's internal Non-Medicinal Ingredient Database, the Natural Health Products Ingredients Database (NHPID) or the Licensed Natural Health Products Database (LNHPD) as a medicinal or a non-medicinal ingredient present in final pharmaceutical products, natural health products or veterinary drugs (DPD 2017; NHPID 2017; LNHPD 2017; personal communication from the Therapeutic Products Directorate, Natural Health Products Directorate and Veterinary Drugs Directorate, Health Canada, to the Risk Management Bureau, Health Canada, dated August 2010; unreferenced). Clary sage essential oil, which naturally contains sclareol, is listed in the NHPID with a medicinal role because it is classified as an NHP substance under item 2 (extract) of Schedule 1 to the *Natural Health Products Regulations* and is listed as a medicinal ingredient in the NNHPD *Aromatherapy – Essential Oils* for use at concentrations up to 5% for topical application, to a maximum of 8% for local application (i.e., up to 10% of

body surface area). It is also listed with a non-medicinal role for oral use as flavour enhancer or for topical use as fragrance ingredient in natural health products (NHPID 2017). It is listed in the Licensed Natural Health Products Database (LNHPD) as being present as such, a medicinal or non-medicinal ingredient, in currently licensed natural health products in Canada (LNHPD 2017). *Salvia sclarea* and other plant species and their preparations that naturally contain sclareol are also listed in the NHPID with a medicinal and/or non-medicinal role and in the LNHPD as being present as such in currently licensed natural health products in Canada (LNHPD 2017; NHPID 2017.

*Salvia sclarea* is native to southern Europe and is commonly cultivated in southern France, Russia, Hungary, Italy, the United Kingdom and the United States (Pitarokili et al. 2002). Extracts of the whole plant, of which sclareol is a constituent, have been used in a variety of applications. Upon hydro-distillation, the flowering inflorescence yields an essential oil that is used in the preparation of various alcoholic beverages (Dzamic et al. 2008). The extract of the aerial part of the *S. sclarea* plant also has a broad spectrum of uses in traditional medicine: analgesic, anti-inflammatory, antioxidant, antifungal, and antibacterial. Fresh leaves of the plant are used in soups (Lattoo et al. 2006). In Greece, *S. sclarea* is known by the common name “agiannitis” and is used locally for coughs, colds, blood cleaning, on wounds and sore eyes, and as a diuretic (Pitarokili et al. 2002).

Sclareol itself is used as a fragrance ingredient in decorative cosmetics, fine fragrances, creams, lotions, shampoos, toilet soaps, and other toiletries, as well as other products used by consumers, such as household cleaners and detergents (Bhatia et al. 2008; Farkas et al. 2005; Ash and Ash 2003, 2006). It has been used for antibacterial activity, fungal-growth regulation (i.e., rust fungi) and plant-growth inhibition (Dimas et al. 2007; Choudhary et al. 2006; Lattoo et al. 2006; Jasinski et al. 2001; Ulubelen et al. 1994; Bailey et al. 1975). Sclareol is used commercially as a fixative in perfumery (ambergris), as a tobacco flavour additive, in foods and beverages, as a synthon for the synthesis of a series of amber odorants, and in traditional medicine (Choudhary et al. 2006; Dimas et al. 2007; Bailey et al. 1975; McChesney and Kouzi 1990; Pitarokili et al. 2002; Kutney and Chen 1994; Leung 1980). Patents have also been developed for the use of sclareol in inducing weight loss and increasing lipolysis (Peele and Dilip 2006). Sclareol is also a precursor for sclareolide, which is another tobacco flavour additive, salt enhancer and a precursor of ambrox, an ambergris-like product used in perfumery (Kutney and Chen 1994; Leung 1980). The Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) has published a specification for sclareol as a food flavouring agent (JECFA 2010a).

# 6. Releases to the environment

There were no reports of use, import or manufacture of sclareol in Canada in 2006 at or above the reporting thresholds specified in the CEPA section 71 notice (Canada 2009b). However, a total estimated quantity of between 76 and 1350 kg sclareol is currently used in Canada per year (see Table 4-1). It is known that sclareol is in commerce in Canada as a component of the clary sage essential oil in cosmetics. The concentration of sclareol in clary sage essential oil has been measured at concentrations ranging from 0.06% to 6%. However, no measured data has been identified for the concentrations of sclareol in cosmetic products. Bhatia et al. have estimated the sclareol concentration in cosmetic products to be 0.03% (2008).

It is expected that the plants producing essential oils containing sclareol will likely be degraded by soil bacteria or other fungal species, as a number of studies have shown soil microorganisms are capable of metabolizing sclareol (see section on Persistence) in its natural terrestrial habitat. However, if sclareol or the essential oil containing sclareol is chemically extracted from these plants and incorporated into various products available to consumers, then down-the-drain releases are likely to occur via wastewater treatment systems[4] (WWTS) effluent into the aquatic environment, where degradation is not likely to occur (see section 7.1).

# 7. Environmental fate

The results of Level III fugacity modelling (Table 7-1) based on the physical and chemical properties of sclareol (Table 3-1) suggest that sclareol is expected to predominantly reside in air, soil or sediment, depending on the compartment of release. These results represent the partitioning of the substance in a hypothetical evaluative environment resulting from intermedia partitioning and loss by both advective transport (out of the modelled region) and degradation/transformation processes. The partitioning values shown in Table 7-1 represent the net effect of these processes under conditions of continuous release when a non-equilibrium “steady-state” has been achieved.

[4] In this assessment, the term “wastewater treatment system” refers to a system that collects domestic, commercial and/or institutional household sewage and possibly industrial wastewater (following discharge to the sewer), typically for treatment and eventual discharge to the environment. Unless otherwise stated, the term wastewater treatment system makes no distinction of ownership or operator type (municipal, provincial, federal, indigenous, private, partnerships). Systems located at industrial operations and specifically designed to treat industrial effluents will be identified by the terms “on-site wastewater treatment systems” and/or “industrial wastewater treatment systems”.

**Table 7-1. Results of the Level III fugacity modelling (EQC 2003) for the percentage of sclareol partitioning into each compartment**

| Substance released to: | Air | Water | Soil | Sediment |
|---|---|---|---|---|
| Air (100%) | 99.9 | 0.005 | 0.004 | 0.12 |
| Water (100%) | 0.02 | 4.1 | 0.0000007 | 96 |
| Soil (100%) | 60 | 0.003 | 40 | 0.07 |

If released to air, high amounts of the substance are expected to reside in air. Given the moderate experimental vapour pressure of 0.1333 Pa and moderate estimated Henry's Llaw constant of 0.315 Pa·$m^3$/mol, sclareol is considered to be moderately volatile. Therefore, if released solely to air, sclareol will almost completely reside in this compartment.

If released to water, sclareol is expected to adsorb to suspended solids and sediment given the moderate estimated log $K_{oc}$ value of 3.1 to 3.4. Volatilization from water surfaces is expected to be a less important fate process because of sclareol's estimated moderate Henry's law constant (0.315 Pa·$m^3$/mol). Thus, if water is a receiving medium, sclareol is expected to partition mainly to sediment.

If released to soil, sclareol is expected to have moderate adsorptivity to soil (i.e., may have some mobility in soil pore waters) given its estimated log $K_{oc}$ (3.1 to 3.4). Because of its estimated Henry's law constant, volatilization from moist soil surfaces seems to be an important fate process. Therefore, if released to soil, sclareol will reside in soil as well as volatilize to air, as illustrated by the results of the Level III-fugacity modelling.

## 7.1 Environmental persistence

Few experimental data are available for sclareol. Consequently, an attempt was made to identify a number of analogues to use in a read-across approach to help determine the persistence and bioaccumulation properties of sclareol. However, no acceptable analogues with measured properties or experimental data were identified.

The structural classes of sclareol (i.e., aliphatic carbons, olefinic carbons, alcohols) are amenable to model predictions as they are considered to be "in the model domain of applicability" (e.g., within structural and/or property parameter domains of the model database). Therefore, the applicability of QSAR models to sclareol is considered appropriate.

Empirical biodegradation in air data for sclareol was available. Vlad and Aryku (1992) investigated the ozonolysis of sclareol under various conditions, such as in ethyl acetate in the presence of pyridine and in ethyl acetate with decomposition of the ozonide in water. The percent yield of the reaction products from 1 g of sclareol ranged from 30% to 52% at temperatures of 18 to 70 °C and an ozonation time of 60 minutes. However, it should be noted that these conditions are not environmentally relevant.

Since few experimental data on the degradation of sclareol are available, a QSAR-based weight-of-evidence approach (Environment Canada 2007) was also applied using the degradation models shown in Table 7-2 below. Sclareol is expected to be released to the water compartment and, given the ecological importance of the water compartment and the fact that most of the available models apply to water; biodegradation in water was primarily examined. Table 7-2 summarizes the results of available QSAR models for degradation in various environmental media.

**Table 7-2. Modelled data for degradation of sclareol**

| Fate process | Type | Model and model basis | Model result and prediction | Extrapolated half-life (days) |
|---|---|---|---|---|
| Atmospheric oxidation | Abiotic | AOPWIN 2008[a] | $t_{½}$ = 0.182 days | < 2 |
| Ozone reaction | Abiotic | AOPWIN 2008[a] | $t_{½}$ = 6.5 days | >= 2 |
| Hydrolysis | Abiotic | HYDROWIN 2008[a] | NA[b] | NA |
| Biodegradation (aerobic) | Primary | BIOWIN 2008[a] Sub-model 4: Expert Survey (qualitative results) | 2.8[c] "does not biodegrade fast" | <=≥ 182 |
| Biodegradation (aerobic) | Ultimate | BIOWIN 2008[a] Sub-model 3: Expert Survey (qualitative results) | 1.7[c] "biodegrades slowly" | >= 182 |
| Biodegradation (aerobic) | Ultimate | BIOWIN 2008[a] Sub-model 5: MITI linear probability | 0.31[d] "31[d] "does not biodegrade fast" | <= 182 |
| Biodegradation (aerobic) | Ultimate | BIOWIN 2008[a] Sub-model 6: MITI non-linear probability | 0.06[d] "biodegrades very slowly" | >= 182 |
| Biodegradation (aerobic) | Ultimate | TOPKAT 2004 Probability | 0[d] "biodegrades very slowly" | >= 182 |
| Biodegradation (aerobic) | Ultimate | CATABOL 2004–2008: % BOD (biological oxygen demand) | 0.3 "biodegrades slowly" | >= 182 |

[a] From EPI Suite (2008), using SMILES notation in Table 2.1 for sclareol
[b] Model does not provide an estimate for this type of chemical structure.
[c] Output is a numerical score from 0 to 5 related to a predicted biodegradation rate.
[d] Output is a probability score.

In air, a predicted atmospheric oxidation half-life value of 0.182 days (see Table 7-2) demonstrates that this substance is likely to be rapidly oxidized. The substance is not expected to react appreciably with other photo-oxidative species in the atmosphere, such as $O_3$, nor is it likely to degrade via direct photolysis given the predicted ozone reaction half-life of 6.5 days (see Table 7-2, AOPWIN 2008). It is therefore expected that reactions with hydroxyl radicals will be the important fate process in the atmosphere for sclareol. With a half-life of 0.182 days via reactions with hydroxyl radicals as the rate-limiting factor overriding the half-life of 6.5 days via ozone reaction, sclareol is considered not to persist in air.

In water, the hydrolysis half-life was not calculable, as no chemicals of structural comparability are contained in the training set of HYDROWIN 2008. In addition, sclareol does not contain functional groups expected to undergo hydrolysis. However, other fate processes in water need to be considered to determine overall persistence in this medium. The empirical 28-day ready biodegradation test result is 1.5% (CHRIP c2008). Most of the biodegradation models suggest that biodegradation is very slow and that the half-life in water would be ≥ 182 days. The substance contains structural features associated with chemicals that are not easily biodegraded (e.g., C-C bonds). Therefore, considering the model results and the structural features of sclareol, there is sufficient evidence to indicate that the biodegradation mineralization half-life of sclareol is > 182 days in water.

Using an extrapolation ratio of 1:1:4 for a water:soil:sediment biodegradation half-life (Boethling et al. 1995), the half-life in soil is also ≥ 182 days and the half-life in sediments is ≥ 365 days. This indicates that sclareol is expected to persist in soil and sediment.

A number of studies have shown that soil micro-organisms are capable of metabolizing sclareol. Kouzi and McChesney (1990, 1991a, 1991b) showed that sclareol was metabolized by six *Cunninghamella* species (mold), three *Aspergillus* species (mold), one *Chaetomium* (mold), *Mucor* species (mold), *Bacillus cereus* (fungus), *Septomyxa* (mold) and *Sporobolomyces* species (fungus). A total of 400 to 600 mg sclareol was dissolved in ethanol, and after 3 to 8 days, the suspensions were filtered and analyzed. Metabolite yields ranged from 28% to 50%. Abraham (1994) showed that many strains of fungi (n=60) and bacteria (n=40) were capable of transforming sclareol, with fungi showing higher metabolic activities than bacteria. *Bacillus sphaericus* ATCC 13805 (fungus) converted 20 mg sclareol over a 72-h period to two metabolites with yields of 5% and 20%. *Cunninghamella elegans* DSM 1908 (mold) converted 200 mg of sclareol after 120 h to five metabolites with yields of 40.5%, 6%, 10%, 2.5%, and 18.5%. *Diplodia gossypina* ATCC 10936 (fungus) converted 10 mg sclareol after 96 h with 20% yields for four metabolites. Aranda et al. (1991) showed the microbial transformation of sclareol by the fungus *Mucor plumbeus*, where 92% to 99% sclareol (up to 0.5 g/L) was consumed within 2 to 4 days. Hanson et al. (1994) showed that the fungus *Cephalosporium aphidicola* microbially transformed sclareol after 12 days into 5 metabolites. Diez et al. (2005) showed the microbial oxidation of 100 mg of sclareol by *Rhizopus stolonifer* (mold) after 5 to 8 days at 30 °C under varying chemical conditions.

The best chemical condition (2.5 g/L $K_2HPO_4$; 2.5 g/L $NH_4NO_3$; 0.25 g/L $MgSO_4$; $10^{-4}$ M $CaCl_2 \cdot 6H_2O$; $1.5x10^{-5}$ M $FeSO_4$; $10^{-5}$ M $MnCl_2$, and 100 mg of sclareol dissolved in ethanol) resulted in the transformation of 87% to 88% of the sclareol after 5 days and 98% of the sclareol after 8 days. Therefore, most of these studies (except for Diez et al. 2005) indicate that the presence of sclareol in soils may be mitigated by the metabolic activities of bacterial and fungal species. However, it should be noted that all of these studies were laboratory-based using media (e.g., liquid medium, agar) other than soil. The described degradation rates may therefore be slower under field conditions.

If sclareol or the essential oil containing sclareol is chemically extracted from these plants and incorporated into various products available to consumers, then down-the-drain releases are likely to occur via wastewater treatment systems into the aquatic environment. No information has been found to indicate that organisms capable of degrading sclareol, similar to those found in soil, are present in surface waters. In addition, under potential anaerobic conditions, such as in sediment, there may be a lack of sufficient aerobic bacteria to facilitate aerobic or anaerobic degradation.

The Transport and Persistence Level III Model (TaPL3) (TaPL3 2000) was used to estimate the characteristic travel distance (CTD), defined as the maximum distance traveled in air by 63% of the substance. Beyer et al. (2000) have proposed CTDs of > 2000 km as representing high long-range atmospheric transport potential (LRATP), 700 to 2000 km as moderate LRATP, and < 700 km as low LRATP. Given the CTD estimate of 91 km, the long-range atmospheric transport potential of sclareol is considered to be low. This means that sclareol is not expected to be transported a significant distance from its emission sources through the atmosphere.

The OECD Pov-LRTP Screening Model can also be used to help identify chemicals with high persistence and long-range transport potential (Scheringer et al. 2006). This is a global model that compartmentalizes the earth into air, water and soil. It is “transport-oriented” rather than “target-oriented,” as it simply identifies the CTD without indicating specifically where a substance may be transported (Fenner et al. 2005). Klasmeier et al. (2006) have suggested that a threshold of 5098 km, based on the model’s CTD estimate for PCB-180, can be used to identify substances with high long-range-transport potential. PCB-180 is empirically known to be found in remote regions. The CTD calculated for sclareol using the OECD model is 47 km, indicating that sclareol has a low potential for transport in air. The empirical and modelled data suggest that sclareol is highly persistent in water and sediment (half-life in water ≥ 182 days and half-life in sediment ≥ 365 days), but not in air (half-life in air ≤ 2 days) or soil (half-life ≤ 365).

## 7.2 Potential for bioaccumulation

Since no experimental bioaccumulation factor (BAF) or bioconcentration factor (BCF) data for sclareol were available, a predictive approach was applied using available BAF and BCF models as shown in Table 7-3 below.

As mentioned previously, the structural classes of sclareol (i.e., aliphatic carbons, olefinic carbons, alcohols) are amenable to model predictions as they are considered to be “in the model domain of applicability” (e.g., within structural and/or property parameter domains of the model database). Therefore, the applicability of QSAR models to sclareol is considered appropriate.

The modelled log $K_{ow}$ value from KOWWIN 2008 was used as it was deemed that this model has the best training set and likely coverage of chemicals similar in structure to sclareol. The modelled log $K_{ow}$ value of 6.0 for sclareol suggests that this chemical has high potential to bioaccumulate in biota (see Table 7-3).

Measures of BAF are the preferred metric for assessing bioaccumulation potential of substances. This is because BCF may not adequately account for the bioaccumulation potential of substances via diet, which predominates for substances with log $K_{ow}$ greater than ~4.0 (Arnot and Gobas 2003). Kinetic mass-balance modelling is, in principle, considered to provide the most reliable prediction method for determining the bioaccumulation potential because it allows for metabolism correction as long as the log $K_{ow}$ of the substance is within the log $K_{ow}$ domain of the model. BCF and BAF estimates, corrected for potential biotransformation, were generated using the BCFBAF model (EPI Suite 2008). Metabolic rate constants were derived using structure activity relationships described further in Arnot et al. (2008a, 2008b, and 2009). Since metabolic biotransformation rate constants are shown to be a function of body weight and temperature (Hu and Layton 2001; Nichols et al. 2006), the BCFBAFWIN model provides a “normalized” kM for a 10-g fish at 15 °C. For sclareol, this screening level kM-QSAR estimate is 0.062 /day. The middle trophic level fish was used to represent overall model output as suggested by the model developer and is generally representative of fish sizes likely to be consumed by most avian or terrestrial piscivores. If the kM for a 10-g fish is scaled to a representative middle trophic level fish (assumed mass ~184 g), the kM is about 0.03/day.

The available evidence indicates that sclareol is expected to bioaccumulate in fish because of its physical and chemical properties (i.e., low water solubility, high log $K_{ow}$). Metabolism-corrected BCF and BAF values range from 4247 to 31 890. On the basis of the available kinetic-based modelled values corrected for metabolism, sclareol is considered to have a high potential to bioaccumulate in fish.

**Table 7-3. Modelled bioaccumulation data for sclareol**

| Test organism | Endpoint | Wet weight (L/kg) | Reference |
|---|---|---|---|
| Fish | BCF | 4247 | BCFBAF 2008 |
| Fish | BCF | 4445 | BCFBAF 2008 |
| Fish | BAF | 31 890 | BCFBAF 2008 |

# 8. Potential to cause ecological harm

## 8.1 Ecological effects assessment

### 8.1.1 Aquatic compartment

There are no available experimental data for aquatic toxicity for this substance; modelled data were therefore used. The structural classes of sclareol (i.e., aliphatic carbons, olefinic carbons, alcohols) are amenable to model predictions as they are considered to be “in the model domain of applicability” (e.g., within structural and/or property parameter domains of the model database). Therefore, the applicability of QSAR models to sclareol is considered appropriate.

A range of aquatic toxicity values were obtained from the various QSAR models. However, a few values were considered to provide unreliable toxicity estimates for this substance, as the predictions indicated that acute effects would be expected at concentrations significantly above its water solubility (i.e., modelled water solubility value is 0.05 mg/L). Given that modelled concentrations for water solubility are often uncertain (a single modelled value in this case), toxicity values that exceeded solubility estimates by up to a factor of 10 were considered to be acceptable. Therefore, the predicted values in Table 8-1 (as indicated) would be considered acceptable. Modelled data for sclareol indicate that this substance is expected to cause acute harm to aquatic organisms at low concentrations (acute median lethal concentrations [$LC_{50}$s] are ≤ 1.0 mg/L).

**Table 8-1. Modelled data for aquatic toxicity for sclareol**

| Test organism | Type of test | Endpoint | Value (mg/L) | Reference |
|---|---|---|---|---|
| Fish | Acute (96 hours) | $LC_{50}$[b] | 0.16[c] | CPOPs 2008 |
| Fish | Acute | $LC_{50}$[b] | 0.04[c] | AIEPS 2003–2007 |
| Fish | (96 hours) | $LC_{50}$[b] | 0.03[c]* | TOPKAT 2004 |
| *Daphnia* | Acute (48 hours) | $LC_{50}$[b] | 0.08[c] | CPOPs 2008 |
| *Daphnia* | Acute (48 hours) | $LC_{50}$[b] | 0.4[c] | AIEPS 2003–2007 |
| *Daphnia* | Acute (48 hours) | $EC_{50}$ | 11.5 | TOPKAT 2004 |
| Algae | Acute (72 hours) | $EC_{50}$[a] | 7.94 | AIEPS 2003–2007 |

[a] $EC_{50}$ – The concentration of a substance that is estimated to cause some effect on 50% of the test organisms.
[b] $LC_{50}$ – The concentration of a substance that is estimated to be lethal to 50% of the test organisms.
[c] Acceptable - given that modelled concentrations for water solubility are often uncertain, toxicity values that exceeded solubility estimates by up to a factor of 10 were considered to be acceptable.
* Value selected for exposure modelling.

### 8.1.2 Other environmental compartments

Choudhary et al. (2006) reported that sclareol exhibits antibacterial activity, fungal growth regulating properties and plant growth inhibiting properties.

Bailey et al. (1974) assayed sclareol for fungal inhibition against *Cladosporium cucumerinum* on silica gel, on agar, and in liquid medium. The diterpene sclareol and 13-epi-sclareol were isolated as a eutectic mixture[4] from the leaves of the *Nicotiana glutinosa* plant. On the silica gel assay, *Cladosporium cucumerinum* growth inhibition occurred at greater than 0.10 mg/cm sclareol. In addition, for the microscope slide assay, the authors found that sclareol up to 500 mg/L did not prevent the germination of spores of several species of fungi (*Alternaria brassicicola, A. longipes, Aspergillus niger, Botrytis cinerea, Cladosporium cucumerinum* and *Colletotrichum lindemuthianum*).

[4] Eutectic describes a mixture that has the lowest freezing point of all combinations of constituents, or the temperature at which this occurs

However, when germinated spores of *Alternaria* sp. were incubated further, it was observed that the colonies produced on agar incorporating sclareol expanded slowly. The effect of sclareol on the growth of mycelium demonstrated that the radial growth rates of 16 species of fungi were significantly reduced at 20 mg/L sclareol. These results suggest that sclareol affects the growth regulatory systems of fungi.

Bailey et al. (1975) investigated the inhibition of fungal growth by an epimeric[5] mixture of the diterpenes, sclareol and 13-episclareol on *Uromyces appendiculatus* (French bean rust), *Puccinia recondita* f. sp. *tritici* (wheat leaf rust) and *Uromyces viciae-fabae* (broad bean rust). The germination of rust uredospores was assessed using the well slide test and a test with agar surfaces impregnated with concentrations of sclareol ranging from 5 to 1000 mg/L. Similar results were obtained with both tests. French bean rust was completely inhibited by 25 mg/L sclareol and its germ tubes were shortened at 5 mg/L. Broad bean rust produced small protuberances at the surface of the uredospores, and normal growth of the germ tube occurred only at levels below 25 mg/L sclareol. Wheat leaf rust had normal growth of the germ tube only if the concentration of sclareol was below 25 mg/L.

Kennedy et al. (1992) used a bioassay to evaluate the effect of sclareol, isolated from the cuticular leaf component of a variety of *Nicotiana* tobacco species (e.g., *Nicotiana tabacum*, *Nicotiana glutinosa*), on the germination of *Peronospora tabacina* (blue mold). Sclareol in acetone was then applied to leaf disks of *Nicotiana tabacum*, which were subsequently inoculated with blue mold sporangia. The $IC_{50}$ for blue mold sporangia inhibition by sclareol was 0.0047 mg/cm$^2$.

Ulubelen et al. (1994) obtained sclareol from an acetone extract of the whole plant *Salvia sclarea* and tested it for antimicrobial activity against standard bacterial strains (*Staphylococcus aureus* and *Proteus mirabilis*) and the yeast *Candida albicans*. Sclareol was found to be active against *Staphylococcus aureus* at 48.25 mg/L and the yeast (no concentration given) but was not active against *Proteus mirabilis*.

**Table 8-2. Empirical microbial and fungal toxicity data for sclareol**

| Test organism | Type of test | Endpoint | Value (mg/L unless otherwise indicated) | Reference |
|---|---|---|---|---|
| Bacterium (*Staphylococcus aureus*) | Acute (24 hours) | Growth inhibition | 48.25 | Ulubelen et al. 1994 |

[5]A type of isomer in which the difference between the two compounds is the relative position of the H (hydrogen) group and OH (hydroxyl) group on the last asymmetric C (carbon) atom of the chain

| Test organism | Type of test | Endpoint | Value (mg/L unless otherwise indicated) | Reference |
|---|---|---|---|---|
| Fungus (*Cladosporium cucumerinum*) | Unknown | Growth inhibition | 0.1 mg/cm | Bailey et al. 1974 |
| Fungus (16 species) | Chronic (10 days) | Mycelium growth | 20 | Bailey et al. 1974 |
| Fungal spores of *Alternaria brassicicola*, *A. longipes*, *Aspergillus niger, Botrytis cinerea*, *Cladosporium cucumerinum, Colletotrichum lindemuthianum* ) | Chronic (10 days) | Spore germination | > 500 | Bailey et al. 1974 |
| Fungus (*Uromyces appendiculatus*) | Unknown | Spore germination and growth | 5 (shortened germ tubes) | Bailey et al. 1975 |
| Fungus (*Uromyces appendiculatus*) | Unknown | Spore germination and growth | 25 (complete inhibition) | Bailey et al. 1975 |
| Fungus (*Uromyces viciae-fabae*) | Unknown | Spore germination and growth | > 25 | Bailey et al. 1975 |
| Fungus (*Puccinia recondita* f. sp. *tritici*) | Unknown | Spore germination and growth | > 25 | Bailey et al. 1975 |
| Blue mold (*Peronospora tabacina*) | Acute (24 hours at 15$^{o}$C) | $IC_{50}$[a] (inhibition of sporangia germination) | 0.0047 mg/cm$^2$ | Kennedy et al. 1992 |

[a] $IC_{50}$ – The inhibiting concentration for a specified percent effect. A point estimate of the concentration of a test substance that causes 50% reduction in a quantitative biological measurement such as growth rate.

## 8.2 Characterization of ecological risk

Sclareol is naturally widespread in the environment as a component in the essential oil of several plants. Sclareol is likely degraded by soil bacteria or other fungal species in their natural terrestrial habitat.

If sclareol or the essential oil containing sclareol is chemically extracted from these plants and then released to the environment through wastewater treatment system releases resulting from industrial and/or consumer uses (estimated total quantity of 76 to 1350 kg/year), sclareol will be found mainly in water and sediment where it is expected to be highly persistent. On the basis of modelled data, sclareol is also expected to have a high bioaccumulation potential in fish and is estimated to be highly hazardous to certain aquatic organisms.

When sclareol is released into a water body, it partitions to suspended particulate matter and to bottom sediments, where sediment-dwelling organisms would be exposed to the substance. However, no environmental monitoring data or toxicity data specific to sediment-dwelling organisms are available for this substance.

Substances that are persistent remain in the environment for a long time after being released, increasing the potential magnitude and duration of exposure. Substances that have long half-lives in mobile media (air and water) and partition into these media in significant proportions have the potential to cause widespread contamination. Releases of small amounts of bioaccumulative substances may lead to high internal concentrations in exposed organisms. Highly bioaccumulative and persistent substances are of special concern, since they may biomagnify in food webs, resulting in very high internal exposures, especially for top predators.

However, given the relatively small amounts known to be in commerce in Canada and its uses which are expected to lead to disperse releases to the environment, ecological exposure to sclareol is expected to be low. It is therefore concluded that sclareol is not currently causing ecological harm in Canada. On the basis of the information available, it is concluded that sclareol is not entering the aquatic 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 a danger to the environment on which life depends.

Although current use patterns and quantities in commerce are not of concern at current levels, there may be concerns if quantities were to increase in Canada, given the ecological effects associated with sclareol.

## 8.3 Uncertainties in evaluation of ecological risk

Given the use of this substance in other countries, it is possible that sclareol is entering the Canadian market as a component of manufactured items and/or products available to consumers (Pitarokili et al. 2002; Lattoo et al.; Choudhary et al. 2006; Dimas et al. 2007; Bailey et al. 1975; McChesney and Kouzi 1990). Information obtained from various information sources indicates that sclareol may be available in a limited number of these types of products in Canada. However, as no information is available on the quantity of sclareol in such imports, it is not possible to derive a quantitative estimate that would help determine the importance of this source.

# 9. Potential to cause harm to human health

## 9.1 Exposure assessment

### 9.1.1 Environmental media and food

Empirical data on concentrations of sclareol in environmental media in Canada were not identified. Sclareol was not reported above the reporting threshold by any single company in response to a CEPA section 71 survey notice for the years 2005 and 2006. However, it is estimated to be used in overall quantities between 76 and 1350 kg. The low use quantities of sclareol indicate that the release into the Canadian environment from industrial and consumer use would be low and exposure of the general population from environmental media is expected to be negligible.

Sclareol is a component of the essential oil in *Salvia sclarea* (clary sage) that may be used as a flavour ingredient in food. It may also be present in common sage, *Salvia officinalis*, which is used as a culinary herb. Several studies that analyzed the composition of common sage were identified in the literature (Santos-Gomes et al. 2001; Perry et al. 1999, 1996; Tucker et al. 1990). Only one study detected sclareol at levels up to 5% (Boszormenyi et al. 2009). JECFA (2010b) recently concluded on the basis of current estimated dietary exposure that sclareol does not pose a safety concern (JECFA 2004). The European Food Safety Authority also concluded that sclareol does not give rise to safety concerns at the level of dietary intake estimated by JECFA.

### 9.1.2 Products available to consumers

#### 9.1.2.1 Cosmetics

Sclareol may be present in several species of sage, but it is predominantly found in *Salvia sclarea* or clary sage (Kuzma et al 2009; Bhatia et al 2008; Dzamic et al. 2008; Farkas et al. 2005; Fraternale et al. 2005; Pitarokili et al. 2002; Ronyai et al. 1999; Esteban et al. 1996; Lawrence 1994, 1986). In Canada, approximately 800 cosmetic products containing the essential oil of clary sage were identified in the Cosmetic Notification System (CNS 2010). According to the information in the CNS database, the concentration of the essential oil in cosmetics ranges from 0.1% to 30%.

The available literature indicates a wide range of sclareol concentrations in clary sage essential oil (from 0.06% [Dzamic et al. 2008] to 6% [Pitarokili et al. 2002]). However, most studies report concentrations of sclareol in essential oil well below 5% (personal communication from the Consumer Product Safety Directorate, Health Canada, to the Risk Management Bureau, Health Canada, dated August 2010; unreferenced). The assumption of 5% of sclareol in essential oil, which can be translated into a range of 0.005% to 1.5% sclareol in products, was used in estimating exposure of the general population from use of cosmetics in Canada. This assumption is considered conservative as information from a cosmetic manufacturer indicates that sclareol is present in cosmetic products at a much lower concentration. Bhatia et al. have estimated the sclareol concentration in cosmetic products to be 0.03% (2008).

Estimates of exposure of the general population of Canada to sclareol from use of cosmetics were derived using ConsExpo 4.1 (ConsExpo 2006).

The upper-bounding estimates of daily exposure from use of cosmetics containing sclareol are presented in Table 9-1, while the details of the exposure scenarios are summarized in Appendix A.

Sclareol has a low vapour pressure, and inhalation exposure is not considered likely except through the use of pump spray. The predominant route of exposure during the use of these products is considered to be dermal. For rinse-off products such as hair shampoo and conditioner, retention factors were applied as appropriate (refer to Appendix A for details). For products in Table 9-1, the predominant contribution to the aggregate exposure was from fragrance ($6.06 \times 10^{-4}$ to 0.404 mg/kg-bw [kilograms of body weight] per day).

**Table 9-1. Estimates of daily dermal exposure from frequently used cosmetics – adults [a]**

| Product | Essential oil concentration range (%)[b] | Sclareol concentration range (%)[c] | Frequency/ yr | Estimated daily dermal exposure (mg/kg-bw per day) |
|---|---|---|---|---|
| Fragrance[d] | 0.1–30 | 0.005–1.5 | 730–1095 | $6.06\times10^{-4}$–0.404 |
| Skin moisturizer (face, hand and/or body) | 0.1–3 | 0.005–0.15 | 730 | $1.69\times10^{-3}$–0.389 |
| Hair shampoo | 0.1–30 | 0.005–0.15 | 260 | $1.02\times10^{-3}$–0.301 |

| Product | Essential oil concentration range (%)[b] | Sclareol concentration range (%)[c] | Frequency/ yr | Estimated daily dermal exposure (mg/kg-bw per day) |
|---|---|---|---|---|
| Hair conditioner | 0.1–30 | 0.005–1.5 | 260 | $6.95\times10^{-4}$–0.209 |
| Facial toner[e] | 0.1–30 | 0.005–0.15 | 365–730 | $8.46\times10^{-4}$–0.106 |
| Hair grooming[f] | 0.1–3 | 0.005–0.15 | 274–438 | $1.12\times10^{-3}$–0.0611 |
| Eye lotion | 0.1–10 | 0.005–0.5 | 365 | $3.52\times10^{-4}$–0.0352 |
| Skin cleanser (face, hand and/or body: bar, liquid) | 0.1–30 | 0.005–1.5 | 329–730 | $8.38\times10^{-6}$–0.0166 |
| Deodorant (stick) | 0.1–1 | 0.005–0.05 | 473 | $1.10\times10^{-3}$–0.0110 |
| Foot deodorant spray | 0.3–1 | 0.015–0.05 | 730 | 0.0584–0.195 |
| Foundation – female only | 0.1–0.3 | 0.005–0.015 | 365 | $5.64\times10^{-4}$–0.0017 |
| Leave-in hair protectant | 0.1–0.3 | 0.005–0.015 | 260 | $6.22\times10^{-4}$–0.0019 |
| Make up removal pads – female only | < 0.1 | 0.005 | 730 | 0.0004 |
| Eye mascara – female only | 0.3–1 | 0.015–0.05 | 365 | $5.29\times10^{-5}$–0.0002 |
| Shaving gel – male only | 0.1–1 | 0.005–0.05 | 365 | $1.41\times10^{-5}$–0.00014 |
| **TOTAL** | **N/A** | **N/A** | **N/A** | **0.0058–1.73[g]** |

**Abbreviations: N/A, not applicable.**
[a] Modelled using ConsExpo 4.1 (RIVM 2006) with default assumptions unless otherwise noted in Appendix A.
[b] Concentrations of the essential oil from clary sage as reported on the Cosmetics Notification System (CNS 2010).
[c] This represents the concentration of sclareol in the cosmetic product, assuming the concentration of sclareol in the essential oil is 5%.
[d] Includes perfume (use frequency assumed to be 730 times per year) and eau de toilette (use frequency assumed to be 1095 times per year).
[e] Includes after shave lotion (use frequency assumed to be 365 times per year) and facial toner (use frequency assumed to be 730 times per year).
[f] Includes mousse (use frequency assumed to be 274 times per year), gel (use frequency assumed to be 358 times per year), hair spray (use frequency assumed to be 438 times per year). The exposure estimates for the hair detangler were added (use frequency assumed to be 438 times per year).
[g] This number does not represent a gender specific estimate. Taking this into account, the range of exposure estimate for female would be 0.0588 to 1.73 mg/kg-bw per day, and for male would be 0.0584 to 1.73 mg/kg-bw per day.

Estimates of exposure to sclareol from cosmetics used less frequently are summarized in Table 9-2. Since these products are used only occasionally, exposure to sclareol from use of these products is considered to be acute in duration. The highest exposure estimate is from use of massage oil, which ranged from 0.00564 to 1.69 mg/kg-bw per use.

**Table 9-2. Estimates of acute dermal exposure from use of cosmetics – adult [a]**

| Product | Essential oil concentration range (%)[b] | Sclareol concentration range (%)[c] | Frequency/yr | Estimated acute dermal exposure (mg/kg-bw)[d] |
|---|---|---|---|---|
| Massage oil | 0.1–30 | 0.005–1.5 | 24 | 0.00564–1.69 |
| Face mask | 0.1–10 | 0.005–0.5 | 104 | 0.00141–0.141 |
| Hair bleach | < 0.1 | 0.005 | 10 | 0.141 |
| Hair dye | 0.3–1 | 0.015–0.05 | 10 | 0.0212–0.0705 |
| Tanning preparation | < 0.1 | 0.005 | 75 | 0.00705 |
| Bath preparation (oil, foam salts) | 0.1–30 | 0.005–1.5 | 104 | $9.17\times10^{-6}$–$2.75\times10^{-4}$ |

[a] Modelled using ConsExpo 4.1 (RIVM 2006) with default assumptions unless otherwise noted in Appendix A.
[b] Concentrations of the essential oil from clary sage as reported on the Cosmetics Notification System (CNS 2010).
[c] Assuming the concentration of sclareol in the essential oil is 5%.
[d] Acute dermal exposure is reported per application.

Estimates of exposure to sclareol from use of cosmetics intended for infants and toddlers are presented in Table 9-3. The upper-bounding estimates of daily exposure ranged from 0.015 to 0.057 mg/kg-bw per day, while for a less frequently used product, i.e., massage oil, the upper-bounding estimate of acute exposure ranged from 0.023 to 0.099 mg/kg-bw.

**Table 9-3. Estimates of chronic and acute dermal exposure from use of cosmetics – infants and toddlers[a,b]**

| Product | Age group | Essential oil concentration range (%)[c] | Frequency /yr | Daily dermal exposure (mg/kg-bw per day) | Estimated acute dermal exposure (mg/kg-bw)[d] |
|---|---|---|---|---|---|
| Baby massage oil | 0–6 month | 0.3–1 | 24 | N/A | 0.0296–0.0987 |
| Baby massage oil | 0.5–4 years | 0.3-1 | 24 | N/A | 0.0232–0.0774 |
| Baby shampoo | 0–6 month | 0.3–1 | 260 | 0.0162–0.0539 | N/A |
| Baby shampoo | 0.5–4 years | 0.3-1 | 365 | 0.0145–0.0483 | N/A |
| Baby body wash | 0–6 month | 0.3–1 | 329 | $8.11\times10^{-4}$–$2.7\times10^{-3}$ | N/A |
| Baby body wash | 0.5–4 years | 0.3–1 | 329 | $6.38\times10^{-4}$–$2.13\times10^{-3}$ | N/A |
| Kids hair detangler | 0–6 month | N/A | N/A | N/A | N/A |
| Kids hair detangler | 0.5–4 years | 0.1–0.3 | 438 | 0.0003–0.0009 | N/A |
| **TOTAL** | **0–6 month** | **-** | **-** | **0.017–0.057** | **N/A** |
| **TOTAL** | **0.5–4 years** | **-** | **-** | **0.015–0.051** | **N/A** |

Abbreviations: N/A, not applicable, '-' no data available
[a] Infants are between 0 and 6 months of age and toddlers are between 0.5 and 4 years of age.
[b] Modelled using ConsExpo 4.1 (RIVM 2006) with default assumptions unless otherwise noted in Appendix A.
[c] Concentrations of the essential oil from clary sage as reported on the Cosmetics Notification System (CNS 2010). The concentration of sclareol in the oil was assumed to be 5%.
[d] Acute dermal exposure is reported per application.

Given the nature of the physical and chemical properties (log $K_{ow}$, molecular weight, $K_p$) of sclareol,, absorption through the skin is expected to be limited. Using an approach developed by Kroes et al. 2007, a default dermal absorption value of 10% was derived.

Lipstick products can contain the essential oil of clary sage at concentrations of 0.1% to 1% wet weight (w/w). Sclareol concentrations in lipstick were therefore estimated to be 0.005% to 0.05%, and daily oral exposure from use of lipstick was estimated to range from $2.82\times10^{-5}$ to $2.82\times10^{-4}$ mg/kg-bw per day (details of the calculation are presented in Appendix A).

Given their use pattern, some cosmetics containing sclareol are considered to result in potential inhalation exposure. Estimates of mean concentration per event from use of products applied as a spray were derived (see Appendix A) and found to be low.

#### 9.1.2.2 Other products

A limited number of natural health products were noted to contain clary sage essential oil as a non-medicinal ingredient. The cosmetic exposure scenarios assessed in the previous section are expected to be representative of exposures from natural health products, considering the conditions of use outlined in the NNHPD Aromatherapy – Essential Oils monograph.

A room mister containing clary sage essential oil as a fragrance ingredient has been identified (CNS 2010). The clary sage essential oil concentration in this product was reported to be 0.3% to 1%; hence the corresponding concentration of sclareol in the product is estimated to be 0.015–0.05%. Based on its use pattern, exposure from use of this product is expected to be mainly via inhalation and the mean event concentration was estimated to range from $2.1\times10^{-4}$ mg/m$^{-3}$ to $6.99\times10^{-4}$ mg/m$^{-3}$ (see Appendix B).

## 9.2 Health effects assessment

Appendix C summarizes the health effects information for sclareol and its analogue, sclareol glycol.

The acute toxicity of sclareol appears to be low, given that the lowest oral and dermal $LD_{50}$ values identified were both greater than 5000 mg/kg-bw in rats and rabbits, respectively (RIFM 1979a, 1979b). Following administration of 100 mg/kg-bw, 316 mg/kg-bw or 1000 mg/kg-bw sclareol via a single intraperitoneal (i.p.) injection to male Sprague-Dawley rats, transient decreases in spontaneous motor activity, a decrease in respiratory rate and a compensatory increase in respiratory depth were observed (Malone et al. 1991).

Undiluted sclareol induced dermal irritation in rabbits at 5000 mg/kg-bw (RIFM 1979a, 1979b), but diluted sclareol did not induce dermal irritation in patch tests or semi-occlusive tests in either human volunteers or rabbits (RIFM 1975a, 1975b; RIFM 1979c; RIFM 1981; RIFM 1986). Sensitization was observed in only one of the human volunteer studies, in which the boiling point of sclareol was 84 to 90 °C, indicating that the purity of the test material was low (RIFM 1979c). Sclareol with a boiling point greater than 96 °C in the other identified sensitization tests in human volunteers did not induce sensitization (RIFM 1981, 1986). The International Fragrance Association (IFRA 2009) identified sensitization as the critical effect of sclareol and set the standard that sclareol used as a fragrance ingredient should have a minimum purity of 98%, on the basis of the results of sensitization tests in human volunteers showing a sensitizing potential for samples with low purity (i.e., low boiling point) and no sensitizing effects for samples with a minimum purity of 98%.

In terms of repeated-dose toxicity, a no-observed-adverse-effect level (NOAEL) of 8.8 mg/kg-bw per day was identified. This was based on the observation of an increase in

mean kidney weight relative to brain weight in male rats and an increase in mean heart and spleen weights relative to brain weight in female rats, when animals were administered sclareol 7 days per week via oral intubation for 30 days at a single dose of 8.8 mg/kg-bw per day. Minimally but statistically increased protein, globulin and calcium concentrations were considered to be possible corroborative clinical chemistry findings with increase in the kidney-to-brain weight ratio for male rats treated with sclareol. These effects maybe treatment related, but were considered non-adverse with limited toxicological significance (RIFM 2006a). RIFM (2006a) identified 8.8 mg/kg-bw per day as a NOAEL because the findings were not consistent between the sexes, and any additional clinical pathological or histopathologic changes such as gross or microscopic alterations or increase in serum liver enzymes in male and female rats were absent.

Very limited genotoxicity data were available for sclareol. Sclareol induced DNA damage in human HCT116 colon cancer cells in vitro. Sclareol suppressed HCT116 tumour growth in immunodeficient male SCID mice that were injected subcutaneously with the maximum tolerated dose (MTD) of 275 mg/kg-bw, which was determined through administration of sclareol encapsulated into the lipid bilayer of liposomes for 5 days (Dimas et al. 2007). In a previous study, sclareol was also reported to induce DNA fragmentation and apoptosis in human leukemic cell lines (Dimas et al. 1999). However, in vitro genotoxicity assays were both negative in a Salmonella/Microsome reversion assay and in a Bacillus subtilis rec-assay on essential oils from clary sage (Salvia sclarea) oil, of which sclareol is a component (Zani et al. 1969; Leung 1980; Lawrence 1986).

After administration to male Wistar rats intravenously at doses of 100 mg/kg-bw and orally via gavage at 1000 mg/kg-bw, 0.02% and 9% of the administered dose was excreted unchanged in bile and feces after intravenous and oral exposure, respectively (Kouzi et al. 1993). Kouzi et al. (1993) also identified four biliary metabolites of sclareol in rats—i.e., 3-keto-sclareol, 3a-hydroxysclareol, 3b-hyroxysclareol and 18-hydroxysclareol—but there is no relevant empirical toxicity data for any of these metabolites.

Since limited health effects information was available for sclareol, information on an analogue substance was also considered. Sclareol glycol (CAS RN 55881-96-4) was found to have structural similarity with sclareol (using the Tanimoto association coefficient in ChemID, the similarity was quantified to be 87.33%).

Sclareol glycol stimulated the locomotor activity of male albino mice exposed to the test substance via a single dose of i.p. injection at 5, 25 or 50 mg/kg-bw, but at 100 mg/kg-bw, it decreased locomotor activity by 30% compared to the controls (Georgieva 1988). It was also reported that sclareol glycol significantly inhibited clonidine-induced aggressive behaviour in male albino mice (Georgieva 1989a). Sclareol glycol administered via i.p. injection stimulated the central nervous system and had dose-dependent effects on convulsive seizures (Georgieva 1987, 1989b). After administration at low dose (5 mg/kg-bw) via i.p. injection, sclareol induced clonic convulsions and myoclonic twitches of the head and forelimbs in 6 of 10 male albino mice (Georgieva

1989b). The route of administration of these studies was of limited relevance to human health risk assessment.

The outputs of predictive (Q)SAR models were considered using four different models, DEREK, TOPKAT, CASETOX and Leadscope Model Applier. The predictions for carcinogenicity, genotoxicity, developmental toxicity, and reproductive toxicity for sclareol were predominantly negative (DEREK 2008; TOPKAT 2004; CASETOX 2008; Leadscope c2005–2008). A summary of the model outputs is shown in Appendix D.

Overall, sclareol was not identified as having high hazard potential.

The confidence in the health effects database for sclareol is low. Only acute, short-term repeated toxicity, irritation and sensitization empirical data were available. No subchronic, chronic/carcinogenicity, in vivo genotoxicity, reproductive or developmental toxicity data were available. Only very limited health effects information was available for an analogue, and (Q)SAR outputs were predominantly negative.

## 9.3 Characterization of risk to human health

On the basis of the available information on use of sclareol, exposure of the general population from environmental media in Canada is expected to be negligible. Dietary exposure of the general population to sclareol is expected to be low and to result mainly from its naturally occurring presence in food.

Dermal exposure to sclareol from the use of cosmetics is considered to be the predominant route of exposure for the general population. Estimates of systemic exposure were derived using the dermal absorption value of 10%. Systemic daily exposure for adults ranges from 0.0058 to 0.173 mg/kg-bw per day. The systemic daily exposure for infants and toddlers ranges from 0.0015 to 0.0057 mg/kg-bw per day.

Comparing the estimates of exposure to sclareol from adult use of cosmetics (0.0058 to 0.173 mg/kg-bw per day) to a level at which no adverse effects were observed in experimental animals (8.8 mg/kg-bw per day) results in margins of exposure ranging from 50 to 1500. Considering that the exposure estimates are based on a series of conservative assumptions (i.e., 10% dermal absorption, 5% sclareol in essential oil coupled with a maximum of 30% essential oil in product, assumption that all types of products would be used on the same day, all containing sclareol at the maximum concentration), actual margins are expected to be much higher than those calculated. Margins would be higher when considering the estimate generated by the Research Institute for Fragrance Materials of 0.0008 mg/kg-bw per day for total human skin exposure from use of multiple cosmetic products containing sclareol (Bhatia et al. 2008). These margins of exposure are considered adequate to address uncertainties in the health effects and exposure databases.

Comparison of the estimates of systemic exposure from use of cosmetics intended for children (0.0015 to 0.0057 mg/kg-bw per day) to a level at which no adverse effects

were observed in experimental animals (8.8 mg/kg-bw per day) results in margins of exposure ranging from 1500 to 5900. These margins are considered adequate to address uncertainties in the health effects and exposure databases.

Comparison of the upper-bounding estimates of acute dermal exposure from less frequent use of cosmetics for adults (0.00564 to 1.69 mg/kg-bw per use) and children (0.023 to 0.099 mg/kg-bw from use of massage oil) to the lowest acute dermal effect level (5000 mg/kg-bw per day based on dermal irritation) results in margins of exposure ranging from $2.96\times10^{3}$ to $8.87\times10^{5}$ for adults and $5.05\times10^{4}$ to $2.17\times10^{5}$ for children. These margins were considered adequate to address uncertainties in the health effects and exposure databases.

Comparison of the upper-bounding estimates of oral exposure from lipstick products ($2.82\times10^{-5}$ to $2.82\times10^{-4}$ mg/kg-bw per day) to a level at which no adverse effects were observed in experimental animals (8.8 mg/kg-bw per day) results in margins of exposure ranging from $9.94\times10^{3}$ to $5.2\times10^{7}$. These margins were considered adequate to address uncertainties in the health effects and exposure databases.

## 9.4 Uncertainties in evaluation of risk to human health

Confidence in the modelled estimates of exposure from products is low to moderate, as direct information on concentrations of sclareol in cosmetic products was not available. There is uncertainty associated with the assumption that sclareol is present in cosmetics mostly from clary sage essential oil. However, on the basis of information in the literature regarding typical use in the cosmetic industry, it is considered to be a reasonable assumption. Also, information regarding the presence of sclareol in food in Canada was not available. The default parameter values in ConsExpo (ConsExpo 2006) were based on upper-bounding scenarios that consider a general population that frequently uses products available to consumers. It is recognized that there is uncertainty with the use of default model parameters that are not Canadian-specific. Uncertainty is also recognized in the use of the approach described by Kroes et al. (2007) to characterize dermal absorption of sclareol once applied as a component in a cosmetic product. As conservative assumptions were used, it is considered likely that derived estimates of general population exposures are considered overestimates (e.g., given the large number of cosmetics on the market, the assumption that an individual would use products that all contained sclareol on the same day is highly conservative).

Because of the very limited empirical health effects database on sclareol and its analogue, and the use of qualitative structure-activity relationship models, confidence in the health effects database is low.

# Conclusion

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from sclareol. It is concluded that sclareol does not meet the criteria under paragraphs 64(*a*)

or 64(*b*) of CEPA as it is 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 available, it is concluded that sclareol does not meet the criteria in paragraph 64(*c*) of CEPA as it is 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 concluded that sclareol does not meet any of the criteria set out in section 64 of CEPA.

# References

Abraham W-R. 1994. Microbial hydroxylation of sclareol. Phytochemistry. 36(6):1421-1424.

ACD/p$K_a$DB [prediction module]. 2005. Ver. 9.04. Toronto (ON): Advanced Chemistry Development. http://www.acdlabs.com/products/phys_chem_lab/pka/. [restricted access].

[AIEPS] Artificial Intelligence Expert Predictive System. 2003–2007. Ver. 2.05. Ottawa (ON): Environment Canada. Model developed by Stephen Niculescu. Available from: Environment Canada, Ecological Assessment Division, New Chemicals Evaluation Section.

[ALOGPS] Octanol-Water Partition Coefficient Program. c2001-2009. Ver. 2.1. Neuherberg (DE): Helmholtz Zentrum Muenchen Institute for Bioinformatics and Systems Biology. http://www.vcclab.org/about/about1.html.

[AOPWIN] Atmospheric Oxidation Program for Microsoft Windows [estimation model]. 2008. Ver. 1.92a. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

Aranda G, Samir El Kortbi M, Lallemand J-Y, Neuman A, Hammoumi A, Facon I, Azerad R. 1991. Microbial transformation of diterpenes; hydroxylation of sclareol, manool, and derivatives by Mucor plumbeus. Tetrahedron. 47(39):8339-8350.

Arnot JA, Gobas FAPC. 2003. A generic QSAR for assessing the bioaccumulation potential of organic chemicals in aquatic food webs. QSAR Comb Sci. 22(3):337-345.

Arnot JA, Mackay D, Bonnell M. 2008a. Estimating metabolic biotransformation rates in fish from laboratory data. Environ Toxicol Chem. 27(2):341-351.

Arnot JA, Mackay D, Parkerton TF, Bonnell M. 2008b. A database of fish biotransformation rates for organic chemicals. Environ Toxicol Chem. 27(11):2263-2270.

Arnot JA, Meylan W, Tunkel J, Howard PH, Mackay D, Bonnell M, Boethling RS. 2009. A quantitative structure-activity relationship for predicting metabolic biotransformation rates for organic chemicals in fish. Environ Toxicol Chem. 28(6):1168-1177.

Ash M, Ash I. 2003. Specialty chemicals source book. 3rd edition**.** Endicott (NY): Synapse Information Resources. SN - 978-1-934764-38-1 AU.

Ash M, Ash I. 2006. Handbook of flavors and fragrances. New York (NY): Synapse Information Resources.

ASTreat Model [wastewater treatment plant removal model]. 2006. Ver. 1.0. Cincinnati (OH): Procter & Gamble Company.

Bailey JA, Vincent GG, Burden RS. 1974. Diterpenes from *Nicotiana glutinosa* and their effect on fungal growth. J Gen Microbiol. 85:57-64.

Bailey JA, Carter GA, Burden RS, Wain RL. 1975. Control of rust diseases from *Nicotiana glutinosa*. Nature. 255: 328-329.

[BCFBAF] Bioaccumulation Program for Microsoft Windows [estimation model]. 2008. Ver. 3.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

Belsito D, Bikers D, Bruze M, Calow P, Greim H, Hanifin JM, Rogers AE, Saurat JH, Sipes IG, Tagami H. 2008. A toxicological and dermatologic assessment of cyclic and non-cyclic terpene alcohols when used as fragrance ingredients. Food Chem Toxicol. 46:S1-S71.

Beyer A, Mackay D, Matthies M, Wania F, Webster E. 2000. Assessing long-range transport potential of persistent organic pollutants. Environ Sci Technol. 34(4):699-703.

Bhatia SP, McGinty D, Letizia CS, Api AM. 2008. Fragrance material review on sclareol. Food Chem Toxicol. 46:S270-S274.

[BIOWIN] Biodegradation Probability Program for Microsoft Windows [estimation model]. 2008. Ver. 4.10. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

Boethling RS, Howard PH, Beauman JA, Larosche ME. 1995. Factors for intermedia extrapolations in biodegradability assessment. Chemosphere. 30(4):741-752.

Boszomenyi A, Hethelyi E, Farkas A, Horvath G, Papp N, Lemberkovics E, Szoke E. 2009. Chemical and genetic relationships among sage (*Salvia officinalis* L.) cultivars and Judean Sage (*Salvia judaica* Boiss.). J Agric Food Chem. 57:4663-4667.

Brouillet L, Coursol F, Favreau M, Anions M. 2010. VASCAN: the database of vascular plants of Canada. [accessed 2010 Nov 9]. http://data.canadensys.net/vascan/.

Canada. [1978a]. *Food and Drug Regulations*, C.R.C., c. 870. http://www.canlii.org/en/ca/laws/regu/crc-c-870/latest/crc-c-870.html.

Canada. [1978b]. *Food and Drug Regulations*, C.R.C., c. 870, s. B.07.034. http://www.canlii.org/en/ca/laws/regu/crc-c-870/latest/crc-c-870.html.

Canada. 1999. *Canadian Environmental Protection Act, 1999*. S.C. 1999, c. 33. Canada Gazette, Part III, vol. 22, no. 3. http://laws-lois.justice.gc.ca/eng/acts/c-15.31/

Canada. 2000. *Canadian Environmental Protection Act, 1999: Persistence and Bioaccumulation Regulations,* P.C. 2000-348, 29 March, 2000, SOR/2000-107, http://laws-lois.justice.gc.ca/eng/regulations/SOR-2000-107/

Canada, Dept. of the Environment, Dept. of Health. 2006a. *Canadian Environmental Protection Act, 1999*: *Notice of intent to develop and implement measures to assess and manage the risks posed by certain substances to the health of Canadians and their environment*. Canada Gazette, Part I, vol. 140, no. 49, p. 4109-4117. http://www.ec.gc.ca/lcpe-cepa/eng/notices/NoticeTypeList.cfm?intCategory=19 http://www.gazette.gc.ca/archives/p1/2006/2006-12-09/pdf/g1-14049.pdf.

Canada, Dept. of the Environment. 2006b. *Canadian Environmental Protection Act, 1999*: *Notice with respect to selected substances identified as priority for action*. Canada Gazette, Part I, vol. 140, no. 9, p. 435-459. http://www.gazette.gc.ca/archives/p1/2006/index-eng.htmlhttp://www.gazette.gc.ca/archives/p1/2006/2006-03-04/pdf/g1-14009.pdf.

Canada, Dept. of the Environment, Dept. of Health. 2009a. *Canadian Environmental Protection Act, 1999: Notice of twelfth release of technical information relevant to substances identified in the Challenge.* Canada Gazette, Part I, vol. 143, no. 52, p. 3839-3843. http://publications.gc.ca/gazette/archives/p1/2009/2009-12-26/pdf/g1-14352.pdf.

Canada, Dept. of the Environment. 2009b. *Canadian Environmental Protection Act, 1999: Notice with respect to Batch 12 Challenge substances.* Canada Gazette, Part I, vol. 143, no. 52, p. 3813-3836. http://publications.gc.ca/gazette/archives/p1/2009/2009-12-26/pdf/g1-14352.pdf.

CASETOX [prediction module]. 2008. Ver 2.0. Beachwood (OH): MultiCASE. http://www.multicase.com/products/prod03.htm [restricted access].

[CATABOL] Probabilistic assessment of biodegradability and metabolic pathways [computer model]. c2004−2008. Ver. 5.10.2. Bourgas (BG): Bourgas Prof. Assen Zlatarov University, Laboratory of Mathematical Chemistry. http://oasis-lmc.org/?section=software&swid=1.

[CFIA] Canadian Food Inspection Agency. 2008. Invasive plants in Canada. Technical report. Ottawa (ON): CFIA. [accessed 2010 Nov 5]. http://www.inspection.gc.ca/english/plaveg/invenv/techrpt/techrese.shtml.

Choudhary MI, Siddiqui ZA, Hussain S, Rahman A-U. 2006. Structure elucidation and antibacterial activity of new fungal metabolites of sclareol. Chem Biodivers. 3:54-61.

[CHRIP] Chemical Risk Information Platform [database]. c2008. Tokyo (JP): National Institute of Technology and Evaluation, Chemical Management Centre (CMC). http://www.safe.nite.go.jp/english/db.html.

[CNS] Cosmetic Notification System [proprietary database]. 2010. Available from Health Canada, Consumer Product Safety Directorate.

[ConsExpo] Consumer Exposure Model. 2006. Ver. 4.1. Bilthoven (NL): Rijksinstituut voor Volksgezondheid en Milieu [National Institute for Public Health and the Environment]. http://www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp#tcm:13-42840.

[CPOPs] Canadian Persistent Organic Pollutants Profiler Model. 2008. Gatineau (QC): Environment Canada, Ecological Assessment Division; Bourgas (BG): Bourgas Prof. Assen Zlatarov University, Laboratory of Mathematical Chemistry. [Model based on Mekenyan et al. 2005].

Cutler HG, Reid WW, Delétang J. 1977. Plant growth inhibiting properties of diterpenes from tobacco. Plant Cell Physiol. 18:711-714.

Demetzos C, Harvala C, Philianos SM, Skaltsounis AL. 1990. A new labdane-type diterpene and other compounds from the leaves of *Cistus incanus* ssp. *creticus*. J Nat Prod. 53(5):1365-1368.

[DEREK] Deductive Estimation of Risk from Existing Knowledge [prediction module on CD ROM]. 2008. Ver. 10.0.2. Cambridge (MA): Harvard University, LHASA Group. http://lhasa.harvard.edu/?page=toxicology.htm [restricted access].

Diez D, Sanchez JM, Rodilla JM, Rocha PM, Mendes RS, Paulino C, Marcos IS, Basabe P, Urones JG. 2005. Microbial hydroxylation of sclareol by *Rhizopus stolonifer*. Molecules. 10:1005-1009.

Dimas K, Kokkinopoulos D, Demetzos C, Vaos B, Marselos M, Malamas M, Tzavaras T. 1999. The effect of sclareol on growth and cell cycle progression of human leukemic cell lines. Leuk Res. 23(3):217-234.

Dimas K, Hatziantoniou S, Tseleni S, Khan H, Georgopoulos A, Alevizopoulos K, Wyche JH, Pantazis P, Demetzos C. 2007. Sclareol induces apoptosis in human HCT116 colon cancer cells in vitro and suppression of HCT116 tumour growth in immunodeficient mice. Apoptosis. 12:685-694.

[DPD] Drug Product Database [database]. 2017. Ottawa (ON): Therapeutic Products Directorate, Health Canada. [accessed 2017]. http://webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp.

Dzamic A, Sokovic M, Ristic M, Grujis-Jovanovic S, Vukojevic J, Marin PD. 2008. Chemical composition and antifungal activity of *Salvia Sclarea* (Lamiaceae) essential oil. Arch Biol Sci Belgrade. 60(2):233-237.

[ECCC, HC] Environment and Climate Change Canada, Health Canada. [modified 2007 Apr 20]. Categorization. Ottawa (ON): Government of Canada. http://www.chemicalsubstanceschimiques.gc.ca/approach-approche/categor-eng.phphttp://www.chemicalsubstanceschimiques.gc.ca/approach-approche/categor-eng.php.

El-Sawi SA, Motawe HM, Ali AM. 2007. Chemical composition, cytotoxic activity and antimicrobial activity of essential oils of leaves and berries of *Juiperus phoenicea* L. grown in Egypt. Afr J Trad Complement Altern Med. 4(4):417-426.

Environment Canada. 1988. Data relating to the Domestic Substances List (DSL) 1984-1986, collected under CEPA, 1988, s. 25(1). Based on: Reporting for the Domestic Substances List [guide] 1988. Data prepared by: Environment Canada.

Environment Canada. 2006. Data for Batch 12 substances collected under the *Canadian Environmental Protection Act, 1999*, section 71: *Notice with respect to certain Batch 12 Challenge substances.* Data compiled by: Environment Canada, Program Development and Engagement Division.

Environment Canada. 2007. Guidance for Conducting Ecological Assessments under CEPA 1999, Science Resource Technical Series, Technical Guidance Module: QSARs. Reviewed Draft Working Document. Gatineau (QC): Environment Canada, Ecological Assessment Division.

Environment Canada. 2010. Data for Batch 12 substances collected under the *Canadian Environmental Protection Act, 1999*, Section 71: *Notice with respect to certain Batch 12 Challenge substances.* Data compiled by: Environment Canada, Program Development and Engagement Division.

Environment Canada, Health Canada. [modified 2007 Apr 20]. Categorization. Ottawa (ON): Government of Canada. http://www.chemicalsubstanceschimiques.gc.ca/approach-approche/categor-eng.phphttp://www.chemicalsubstanceschimiques.gc.ca/approach-approche/categor-eng.php.

[EPI Suite] Estimation Programs Interface Suite for Microsoft Windows [estimation model]. 2008. Ver. 4.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

[EQC] Equilibrium Criterion Model. 2003. Ver. 2.02. Peterborough (ON): Trent University, Canadian Centre for Environmental Modelling and Chemistry. http://www.trentu.ca/academic/aminss/envmodel/models/EQC2.html.

Esteban JL, Martinez-Castro I, Morales R, Fabrellas B, Sanz J. 1996. Rapid identification of volatile compounds in aromatic plants by automatic thermal desorption – GC-MS. Chromatographia. 43:63-72.

European Commission. 2002. *Sclareol.* Commission Decision 2002/113/EC of 23 January 2002 amending Commission Decision 1999/217/EC as regards the register of flavouring substances used in or on foodstuffs. Official Journal of the European Union 20.2.2002. L 49/1. [accessed 2010 Aug]. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:049:0001:0160:EN:PDF.

Farkas P, Holla M, Tekel J, Mellen S, Vaverkova S. 2005. Composition of the essential oils from the flowers and leaves of *Salvia sclarea* L. (Lamiaceae) cultivated in Slovak Republic. J Essent Oil Res. 17:141-144.

Fenner K, Scheringer M, MacLeod M, Matthies M, McKone TE, Stroebe M, Beyer A, Bonnell M, Le Gall A, Klasmeier J, Mackay D, Pennington DW, Scharenberg B, Wania F. 2005. Comparing estimates of persistence and long-range transport potential among multimedia models. Environ Sci Technol. 39:1932-1942.

Fraternale D, Giamperi L, Bucchini A, Ricci D, Epifano F, Genovese S, Curini M. 2005. Composition and anti-fungal activity of essential oil of *Salvia sclarea* from Italy. Chem Nat Comp. 41(5):604-606.

Georgieva JV. 1987. General activity and toxicity of the diterpene sclareol glycol. Contemporary Problems of Experimental and Clinical Oncology 1987:51-56 [cited in Georgieva 1989b].

Georgieva JV. 1988. Effects of the diterpene sclareol glycol on the locomotor activity. C R Acad Bulg Sci. 41(9):139-142.

Georgieva JV. 1989a. Diterpene sclareol glycol inhibits clonidine-induced aggressive responses in mice. Pharmacol Biochem Behav. 34(3):503-505.

Georgieva JV. 1989b. Effects of the diterpene sclareol glycol on convulsive seizures. Methods Find Exp Clin Pharmacol. 11(5):335-340.

Hanson JR, Hitchcock PB, Nasir H, Truneh A. 1994. The biotransformation of the diterpenoid, sclareol, by *Cephalosporium aphidicola*. Phytochemistry. 36(4):903-906.

Health Canada. 1995. Investigating human exposure to contaminants in the environment: A handbook for exposure calculations. Ottawa (ON): Health Canada.

Health Canada. 2010. The cosmetic ingredient hotlist – September 2009. Ottawa (ON): Health Canada, Consumer Product Safety Directorate. [accessed 2010 Jul]. http://www.hc-sc.gc.ca/cps-spc/person/cosmet/info-ind-prof/hot-list-critique/hotlist-liste-eng.php.

Health Canada 2013. Food and Drugs Act – Lists of Permitted Food Additives.

[HENRYWIN] Henry's Law Constant Program for Microsoft Windows [estimation model]. 2008. Ver. 3.20. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

Hu TM, Layton WL. 2001. Allometric scaling of xenobiotic clearance: uncertainty versus universality. AAPS PharmSci. 3(4):E29.

[HYDROWIN] Hydrolysis Rates Program for Microsoft Windows [estimation model]. 2008. Ver. 2.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

[IFRA] International Fragrance Association. 2009. IFRA standard specification: sclareol. International Fragrance Association. http://www.ifraorg.org/files/documentspublished/1/en-us/STSP/22138_STSP_2009_11_04_Sclar%C3%A9ol.pdf.

Jasinski M, Stukkens Y, Degand H, Purnelle B, Marchand-Brynaert J, Boutry M. 2001. A plant plasma membrane ATP Binding cassette-type transporter is involved in antifungal terpenoid secretion. Plant Cell. 13(5):1095-1107.

[JECFA] Joint FAO/WHO Expert Committee on Food Additives. 2004. Safety evaluation of certain food additives and contaminants. WHO Food Additives Series No. 52. [accessed 2010 Oct 13]. http://www.who.int/ipcs/publications/jecfa/monographs/en/.

[JECFA] Joint FAO/WHO Expert Committee on Food Additives. 2010a. Specifications for flavourings. [accessed 2010 Oct 13]. http://www.fao.org/ag/agn/jecfa-flav/details.html?flavId=7030.

[JECFA] Joint FAO/WHO Expert Committee on Food Additives. 2010b. Seventy-third meeting, Geneva, 8-17 June 2010. Summary and Conclusions, Issued 24 June 2010. [accessed 2010 Oct 13]. http://www.who.int/foodsafety/publications/chem/summary73.pdf.

Jermstad A. 1927. The physical constants and chemical properties of the concrete oil of *Salvia sclarea* L. and its principal constituent, sclareol. Pharm Acta Helv. 2:182-190;.

Kennedy BS, Nielsen MT, Severson RF, Sisson VA, Stephenson MK, Jackson SM. 1992. Leaf surface chemicals from *Nicotiana* affecting germination of *Peronospora tabacina* (adam) *sporangia*. J Chem Ecol. 18(9):1467-1479.

Klasmeier J, Matthies M, MacLeod M, Fenner K, Scheringer M, Stroebe M, Le Gall AC, McKone TE, van de Meent D, Wania F. 2006. Application of multimedia models for screening assessment of long-range transport potential and overall persistence. Environ Sci Technol. 40:53-60.

[KOAWIN] Octanol Air Partition Coefficient Program for Microsoft Windows [estimation model]. 2008. Ver. 1.10. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

[KOCWIN] Soil Adsorption Coefficient Program [estimation model]. 2008. Ver. 2.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. www.epa.gov/oppt/exposure/pubs/episuite.htm.

Kolak U, Hacibekiroğlu I, Öztürk M, Özgökçe F, Topçu G, Ulubelen A. 2009. Antioxidant and anticholinesterase constituents of *Salvia poculata*. Turk J Chem. 33:813-823.

Kouzi SA, McChesney JD. 1990. Microbial metabolism of the diterpene sclareol: oxidation of the A ring by *Septomyxa affinis*. Helv Chim Acta. 73:2157-2164.

Kouzi SA, McChesney JD. 1991a. Microbial models of mammalian metabolism: fungal metabolism of the diterpene sclareol by *Cunninghamella* species. J Nat Prod. 54(2):483-490.

Kouzi SA, McChesney JD. 1991b. Hydroxylation and glucoside conjugation in the microbial metabolism of the diterpene sclareol. Xenobiotica. 21(10):1311-1323.

Kouzi SA, McChesney JD, Walker LA. 1993. Identification of four biliary metabolites of the diterpene sclareol in the laboratory rat. Xenobiotica. 23:621-632.

[KOWWIN] Octanol-Water Partition Coefficient Program for Microsoft Windows [estimation model]. 2008. Ver. 1.67. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

Kroes R, Renwick AG, Feron V, Galli CL, Gibney M, Greim H, Guy RH, Lhuguenot JC, van de Sandt JJM. 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem Toxicol. 45:2533-2562.

Kutney JP, Chen Y. 1994. The chemistry of thujone. XVII. The synthesis of ambergris fragrances and related analogues. Can J Chem. 72:1570-1581.

Kuzma L, Kalemba D, Rozalski M, Rozalska B, Wieckowska-Szakiel M, Krajewska U, Wysokinska H. 2009. Chemical composition and biological activities of essential oil from *Salvia sclarea* plants regenerated *in vitro*. Molecules. 14:1438-1447.

Lattoo SK, Dhar RS, Dhar AK, SharmaPR, Agarwal SG. 2006. Dynamics of essential oil biosynthesis in relation to inflorescence and glandular ontogeny in *Salvia sclarea*. Flavour Fragr J. 21:817-821.

Lawrence BM. 1986. Progress in essential oils: clary sage oil. Perfumer & Flavorist. 11:111-118.

Lawrence BM. 1994. Production of clary sage oil and sclareol in North America. Proc. of Remes Recontres Internationales Nyons pp. 41-48.

Leadscope Enterprise [data management and decision support platform]. c2005−2008. Ver. 2.4.15. Columbus (OH): Leadscope Inc. [accessed 2010 Jul 27]. http://www.leadscope.com/lse_product.php [restricted access].

Leung AY. 1980. Encyclopedia of common natural ingredients used in food, drugs and cosmetics. 1st. ed. New York (NY): John Wiley.

[LNHPD] Licensed Natural Health Products Database [database]. 2017. Natural and Non-prescription Health Products Directorate, Health Canada. [accessed 2017]. http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/lnhpd-bdpsnh-eng.php.

LookChem.com. 2008. Sclareol CAS RN 515-03-7. Hangzhou (CN) [accessed 2010 Aug 9]. http://www.lookchem.com/cas-515/515-03-7.html.

Malone MH, McChesney JD, Kouzi SA. 1991. A pharmacological evaluation of the diterpene (-)-sclareol in intact rats. Fitoterapia. 62(2):123-129.

McChesney JD, Kouzi SA. 1990. Microbial models of mammalian metabolism: sclareol metabolism. Planta Med. 56:693.

Mekenyan G, Dimitrov SD, Pavlov TS, Veith GD. 2005. POPs: A QSAR system for creating PBT profiles of chemicals and their metabolites. SAR QSAR Environ Res. 16(1-2):103-133.

[NCI] National Chemical Inventories [database on CD-ROM]. 2007. Issue 1. Columbus (OH): American Chemical Society. [accessed 2009 Aug 11]. http://www.cas.org/products/cd/nci/index.html.

[NHPID] Natural Health Products Ingredients Database [database]. 2017. Natural and Non-prescription Health Products Directorate, Health Canada. [accessed 2017]. http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/online-enligne/nhpid-bipsn-eng.php.

Nichols JW, Fitzsimmons PN, Burkhard LP. 2007. In vitro – in vivo extrapolation of quantitative hepatic biotransformation data for fish. II. Modeled effects on chemical bioaccumulation. Environ Toxicol Chem. 26:1304-1319.

[NRCS] Natural Resources Conservation Service. 2010. The Plants Database. Baton Rouge (LA): United States Department of Agriculture, NRCS. [accessed 2010 Nov 5]. http://plants.usda.gov.

[NWCB] Washington State Noxious Weed Control Board. 2008. Class A noxious weed, clary sage, *Salvia sclarea*. Olympia (WA): Washington State NWCB. [accessed 2010 Nov 5]. http://www.nwcb.wa.gov/weed_info/Salvia_sclarea.html.

[OECD] Organisation for Economic Co-operation and Development. 2010. Emission scenario document on the blending of fragrance oils into commercial and consumer products. Paris (FR): OECD Environmental Directorate, Environmental Health and Safety Division. ENV/JM/MONO(2010)38, JT03287706 [accessed 2010 Nov 23]. http://www.oecd.org/dataoecd/39/2/46021591.pdf.

Peana AT, Moretti MDL, Juliano C. 1999. Chemical composition and antimicrobial action of the essential oils of *S. desoleana* and *S. sclarea*. Planta Med. 65:752-754.

Peele and Dilip. 2006. Compositions comprising sclareol or a derivative thereof bound to a glycoprotein matrix, and therapeutic matrix thereof. Avoca Inc. USA. Patent No. WO 2005-US40212 200551107.

Perry NB, Baxter AJ, Brennan NJ, van Klink JW. 1996. Dalmatian Sage. Part 1. Differing Oil Yields and Compositions from Flowering and Non-Flowering Accessions. Flavour Fragr J. 11:231-238.

Perry NB, Anderson RE, Brennan NJ, Douglas MH, Heaney AJ, McGimpsey JA, Smallfield BM. 1999. Essential oils from Dalmatian sage (*Salvia officinalis* L.): variations among individuals, plant parts, seasons, and sites. J Agric Food Chem. 47:2048-2054.

Piozzi F, Bruno M. 2009. Diterpenoids in the essential oils from the genus *Stachys*. Rec Nat Prod. 3(3):120-125.

Pitarokili D, Couladis M, Petsikos-Panayotarou N, Tzakou O. 2002. Composition and antifungal activity on soil-borne pathogens of the essential oil of *Salvia sclarea* from Greece. J Agric Food Chem. 50:6668-6691.

[RIFM] Research Institute for Fragrance Materials, Inc. 1975a. Repeated insult patch test with sclareol. Unpublished report from Givaudan, 17 June. Report number 45024. Woodcliff Lake (NJ): RIFM [cited in Belsito et al. 2008].

[RIFM] Research Institute for Fragrance Materials, Inc. 1975b. Repeated insult patch test with sclareol. Unpublished report from Givaudan, 18 June. Report number 45025. Woodcliff Lake (NJ): RIFM [cited in Belsito et al. 2008].

[RIFM] Research Institute for Fragrance Materials, Inc. 1979a. Acute toxicity study in rats and rabbits. Report number 1924, May 31. Woodcliff Lake (NJ): RIFM [cited in Bhatia et al. 2008].

[RIFM] Research Institute for Fragrance Materials, Inc. 1979b. Acute toxicity study in rats and rabbits. Report number 1697, April 20. Woodcliff Lake (NJ): RIFM. [cited in Bhatia et al. 2008].

[RIFM] Research Institute for Fragrance Materials, Inc. 1979c. Report on human maximization studies. Report number 1697, April to November. Woodcliff Lake (NJ): RIFM [cited in Belsito et al. 2008].

[RIFM] Research Institute for Fragrance Materials, Inc. 1981. Report on human maximization studies. RIFM Report Number 1792, March 18. Woodcliff Lake (NJ): RIFM [cited in Belsito et al. 2008].

[RIFM] Research Institute for Fragrance Materials Inc. 1986b. Report on human maximization studies. RIFM Report Number 3100, January 15. Woodcliff Lake (NJ): RIFM. [cited in Belsito et al. 2008].

[RIFM]. Research Institute for Fragrance Materials. 1992. Fragrance raw materials monographs. Sclareol. Food Chem Toxicol. 30:115S.

[RIFM] Research Institute for Fragrance Materials, Inc. 2006a. Sclareol and cedrol: subchronic toxicity study (28 day repeated dose oral gavage study in rats). Unpublished report from FEMA. Report number 50942 (RIFM, Woodcliff Lake (NJ). (cited in Bhatia et al. 2008).

[RIVM] Rijksinstituut voor Volksgezondheid en Milieu [National Institute for Public Health and the Environment]. 2006. Cosmetics fact sheet: to assess the risks for the consumer: updated version for ConsExpo 4. Bilthoven (NL): RIVM. Report No.: 320104001/2006. [accessed 2010 Aug]. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf.

Ronyai E, Simandi B, Lemberkovics E, Veress T, Patiaka D, 1999. Comparison of the volatile composition of clary sage oil obtained by hydro distillation and supercritical fluid extraction. J Essent Oil Res. 11:69-71.

Santos-Gomes PC, Fernandes-Ferreira M. 2001. Organ- and season-dependent variation in the essential oil composition of *Salvia officinalis* L. cultivated at two different sites. J Agric Food Chem. 49:2908-2916.

Scheringer M, MacLeod M, Wegmann F. 2006. The OECD $P_{OV}$ and LRTP Screening Tool. Vers. 2.0. Organisation for Economic Cooperation and Development. Zurich (CH): Swiss Federal Institute of Technology. Distributed at OECD/UNEP Workshop on Application of Multimedia Models for Identification of Persistent Organic Pollutants, Ottawa, Canada, May 31 – June 2, 2006. www.sust-chem.ethz.ch/downloads/Tool2_0_Manual.pdf.

Schmiderer C, Grassi1 P, Novak J, Weber M, Franz C. 2008. Diversity of essential oil glands of clary sage (*Salvia sclarea* L., Lamiaceae). Plant Biol. 10:433-440.

Senatore F, Formisano C, Arnold NA, Piozzi F. 2005. Essential oils from *Salvia* sp. (Lamiaceae). III. Composition and antimicrobial activity of the essential oil of *Salvia palaestina* Benth. Growing wild in Lebanon. J Essent Oil Res. 17:419-421.

Sigma-Aldrich Material Safety Data Sheets. 2010. Sclareol CAS RN 515-03-7. St. Louis (MO) [accessed 2010 Aug 9]. http://www.sigmaaldrich.com/catalog/ProductDetail.do?lang=en&N4=357995|ALDRICH&N5=SEARCH_CONCAT_PNO|BRAND_KEY&F=SPEC.

Sirikanataramas S, Yamazaki M, Saito K. 2008. Mechanisms of resistance to self-produced toxic secondary metabolites in plants. Phytochem Rev. 7:467-477.

Smith RL, Waddell WJ, Cohen SM, Feron VJ, Marnett LJ, Portoghese PS, Rietjens IMCM, Adams TB, Taylor S, Gavin CL, McGowen MM, Williams MC. 2009. GRAS flavoring substances 24. Food Technol. 63(6):46-105. [accessed 2010 Jul]. http://www.femaflavor.org/GRAS%2024.pdf.

Soković MD, Brkić DD, Džamić AM, Ristić MS, and Marin PD. 2009. Chemical composition and antifungal activity of *Salvia desoleana* Atzei & Picci essential oil and its major components. Flavour Fragr J. 24:83-87.

Souleles C, Argyriadou N. 1997. Constituents of the essential oil of *Salvia sclarea* growing wild in Greece. Int J Pharmacogn. 35(3): 218-220.

Surburg H, Panten J. 2006. Common fragrance and flavour materials, preparation, properties and uses. 5th ed. Weinheim (DE): Wiley-Vch verlag GmbH & Co. kGaA. p. 229.

[TaPL3] Long Range Transport and Persistence Level III Model. 2000. Ver. 2.10. Peterborough (ON): Trent University, Canadian Centre for Environmental Modelling and Chemistry. http://www.trentu.ca/academic/aminss/envmodel/models/TaPL3.html.

[TOPKAT] TOxicity Prediction by Komputer Assisted Technology. 2004. Ver. 6.2. San Diego (CA): Accelrys Software Inc. http://www.accelrys.com/products/topkat/index.html.

Tucker AO, Maciarello MJ. 1990. Essential oils of cultivars of Dalmatian sage (*Salvia officinalis* L.). J Essent Oil Res. 2:139-144.

Tutin TG, Heywood VH, Burges NA, Moore BM, Valentine DH, Walters SM, Webb DA. 1972. Flora Europea, III London (UK): Cambridge University. [cited in Souleles and Argyriadou 1997].

Ulubelen A, Topcu G, Eris C, Sonmez U, Kartal M, Kurucu S, Bozok-Johansson C. 1994. Terpenoids from *Salvia sclarea*. Phytochemistry. 36(4):971-974.

[US EPA] United States Environmental Protection Agency. 1986.

Vlad PF, Aryku AN. 1992. Investigation of the products of the ozonolysis of sclareol and the pathways for their formation. Institute of Chemistry, Academy of Sciences of the Moldavian SSR, Kishenev. 4:502-511.

[WSKOWWIN] Water Solubility for Organic Compounds Program for Microsoft Windows [estimation model]. 2008. Ver. 1.41. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

Zani F, Massimo G, Benvenuti S, Bianchi A, Albasini A, Melegari M, Vampa G, Bellotti A, Mazza P. 1969. Studies on the genotoxic properties of essential oils with Bacillus subtilis rec-Assay and Salmonella/microsome reversion assay. Planta Med. 57:237-241.

# Appendices

### Appendix A – Upper bounding estimates of exposure to Sclareol in Cosmetics using ConsExpo 4.1 (ConsExpo 2006)

The following notes pertain to the data of the Appendices A-1 to A-6:

1. The following assumptions were applied to all scenarios:
   - body weight of 70.9 kg for an adult
   - uptake fraction of 1 was used to account for external applied dose
   - exposure type of “direct dermal contact” for instant application (ConsExpo 2006)
   - concentrations of the essential oil as reported on the Cosmetics Notification System (CNS 2010)
   - concentration of sclareol in essential oil of 5%.
2. Essential oil concentration range, Exposure frequency, Exposed area and Product amount applied are all default ConsExpo assumptions (RIVM 2006).
3. The Exposed Area data is referenced from Health Canada 1995.
4. External applied dose: Chronic external applied dose calculated through amortization over a year to estimate daily exposure dose.
5. Retention factor was applied for rinse-off products (Cosmetics Exposure Workbook, New Substances Assessment and Control Bureau, Health Canada, 2006; unreferenced).
6. Deposition factor of 10% was applied for those products used in the hair, but not directly on the scalp (ConsExpo 2006).
7. The amounts of product applied for: Skin moisturizer, hair conditioner, skin cleanser for face, facial wash and leave-in hair protectant were calculated by multiplying the product amounts as stated in RIVM (2006) by the ratio of the surface area of the affected body surface as reported in Health Canada (1995) with that of RIVM (2006).

## Appendix A-1. Chronic exposure estimates of adult exposure via the dermal route

1. Fragrance- Perfume

   Scenario: Fragrance

   Assumptions:
   Essential oil concentration (%): 0.1–30
   Exposure frequency (times/year): 730–1095
   Exposed area ($cm^2$): 100 (Health Canada 1995)
   Product amount applied (g): 100 (note: This scenario includes perfume (use frequency assumed to be 730 times per year and the amount of product applied is 0.43 g) and eau de toilette (use frequency assumed to be 1095 times per year and the amount of product applied is 0.64 g)).
   External applied dose (g): 0.43–0.64

   External applied dose[b] (mg/kg-bw per day): $6.06 \times 10^{-4}$–0.404

2. Skin moisturizer face, hand and/or body cream

   Scenario: skin moisturizer

   Assumptions:
   Essential oil concentration (%):0.1–3
   Exposure frequency (times/year):730
   Exposed area ($cm^2$): (Health Canada 1995): 637–1.76E4
   Product amount applied (g):1.2–9.2

   External applied dose: $1.69 \times 10^{-3}$–0.389

3. Hair shampoo

   Scenario: hair shampoo

   Assumptions
   Essential oil concentration (%): 0.1–30
   Exposure frequency (times/year):260
   Exposed area ($cm^2$): 1.55E3 (Health Canada 1995)
   Retention factor of 10% was applied
   Product amount applied (g): 60

   External applied dose: $1.02 \times 10^{-3}$–0.301

4. Hair conditioner

   Scenario: hair conditioner

Assumptions
Essential oil concentration (%): 0.1–30
Exposure frequency (times/year): 260
Exposed area ($cm^2$): 1.55E3 (Health Canada 1995)
Deposition factor of 10% was applied
Product amount applied (g): 54

External applied dose: $6.95 \times 10^{-4}$–0.209

5. Shaving preparation

Scenario: after shave lotion

Assumptions
Essential oil concentration (%):<0.1–0.1
Exposure frequency (times/year): 365
Exposed area ($cm^2$): 319 (Health Canada 1995)
Product amount applied (g): 1.2

External applied dose: $8.46 \times 10^{-4}$

6. Facial toner

Scenario: cleansing lotion

Assumptions
Essential oil concentration (%): 0.1–3
Exposure frequency (times/year): 730
Exposed area ($cm^2$): 637 (Health Canada 1995): 637
Product amount applied (g): 2.5

External applied dose: $3.52 \times 10^{-3}$–0.106

7. Hair spray

Scenario: hair spray

Assumptions
Essential oil concentration (%): 0.1–0.3
Exposure frequency (times/year): 438
Exposed area ($cm^2$): (Health Canada 1995): 637
Retention factor of 20% was applied
Product amount applied (g): 0.6

External applied dose: $1.01 \times 10^{-4}$–$3.04 \times 10^{-4}$

8. Hair grooming

   Scenario: hair gel

   Assumptions
   - Essential oil concentration (%): 0.1–0.3
   - Exposure frequency (times/year): 274
   - Exposed area ($cm^2$): 637 (Health Canada 1995)
   - Product amount applied (g): 0.3

   External applied dose: $1.59 \times 10^{-4}$–$4.76 \times 10^{-4}$

9. Hair detangler

   Scenario: hair spray with trigger bottle

   Assumptions
   - Essential oil concentration (%): <0.1
   - Exposure frequency (times/year): 438
   - Exposed area ($cm^2$): 637 (Health Canada 1995)
   - Product amount applied (g): 0.6

   External applied dose: $1.04 \times 10\text{-}^{3}$

10. Hair grooming

    Scenario: hair gel

    Assumptions
    - Essential oil concentration (%): 0.1–3
    - Exposure frequency (times/year): 358
    - Exposed area ($cm^2$): 637 (Health Canada 1995)
    - Product amount applied (g): 0.3

    External applied dose: $2.07 \times 10^{-4}$–0.061

11. Eye lotion

    Scenario: eye make-up remover

    Assumptions
    - Essential oil concentration (%): 0.1–10
    - Exposure frequency (times/year): 365
    - Exposed area ($cm^2$): (Health Canada 1995): 50
    - Product amount applied (g): 0.5

External applied dose: $3.52 \times 10^{-4}$–0.0352

12. Skin cleanser for face, hand and/or body (bar, liquid)

Scenario: skin cleanser

Assumptions
- Essential oil concentration (%): 0.1–30
- Exposure frequency (times/year): 329–730
- Exposed area ($cm^2$): 637-1.76E4$cm^2$ (Health Canada 1995)
- Retention factor of 1% as applied
- Product amount applied (g): 1.78–26.2

External applied dose: $8.38 \times 10^{-6}$–0.0166

13. Deodorant stick

Scenario: Deodorant

Assumptions
- Essential oil concentration (%): 0.1–1
- Exposure frequency (times/year): 473
- Exposed area ($cm^2$): 240 (estimate) (Health Canada 1995)
- Product amount applied (g): 1.2

External applied dose: $1.10 \times 10^{-3}$ – $1.1 \times 10^{-2}$

14. Foot deodorant spray

Scenario: trigger spray

Assumptions
- Essential oil concentration (%): 0.3–1
- Exposure frequency (times/year): 730
- Exposed area ($cm^2$): 1280 (Health Canada 1995)
- Product amount applied (g): 13.8

External applied dose: 0.0584–0.195

15. Facial wash

Scenario: makeup removal pads

Assumptions
- Essential oil concentration (%): <0.1
- Exposure frequency (times/year): 730

Exposed area ($cm^2$): 637 (Health Canada 1995)
Retention factor of 10% was applied
Product amount applied (g): 2.5

External applied dose: $5.64 \times 10^{-4}$–$1.69 \times 10^{-3}$

16. Leave-in hair protectant

Scenario: hair conditioner (no retention factor)

Assumptions
Essential oil concentration (%): 0.1–0.3
Exposure frequency (times/year): 260
Exposed area ($cm^2$): 1.44E3 $cm^2$ (Health Canada 1995)
Deposition factor of 10% was applied
Product amount applied (g): 12.4

External applied dose: $6.22 \times 10^{-4}$–$1.9 \times 10^{-3}$

17. Face makeup – foundation

Scenario: facial makeup

Assumptions
Essential oil concentration (%): 0.1–3
Exposure frequency (times/year): 365
Exposed area ($cm^2$): 637 (Health Canada 1995)
Product amount applied (g): 0.8

External applied dose: $3.52 \times 10^{-4}$

18. Eye mascara

Scenario: eye makeup

Assumptions
Essential oil concentration (%): 0.3–1
Exposure frequency (times/year): 365
Exposed area ($cm^2$): 1.6 (Health Canada 1995)
Product amount applied (g): 0.025

External applied dose: $5.29 \times 10^{-5}$ – $1.76 \times 10^{-4}$

19. Shaving preparation gel

Scenario: shaving cream

Assumptions
- Essential oil concentration (%): 0.1–1
- Exposure frequency (times/year): 365
- Exposed area ($cm^2$): 318 (Health Canada 1995)
- Product amount applied (g): 2

External applied dose: $1.41 \times 10^{-5} – 1.41 \times 10^{-4}$

## Appendix A-2. Acute exposure estimates of Adults via the dermal route

1. Massage oil

   Scenario: massage oil

   Assumptions
   - Essential oil concentration (%): 0.1–30
   - Exposure frequency (times/year): 24
   - Exposed area ($cm^2$): 1.68E4 (Health Canada 1995)
   - Product amount applied (g): 8

   External applied dose (mg/kg-bw): $5.64 \times 10^{-3}$–1.69

2. Hair bleach

   Scenario: hair bleach

   Assumptions
   - Essential oil concentration (%): <0.1
   - Exposure frequency (times/year): 10
   - Exposed area ($cm^2$): 637 (Health Canada 1995)
   - Product amount applied (g): 200
   - External applied dose (mg/kg-bw): 0.141

3. Purifying mask

   Scenario: face mask

   Assumptions
   - Essential oil concentration (%): 0.3–1
   - Exposure frequency (times/year): 104
   - Exposed area ($cm^2$): 637 (Health Canada 1995)
   - Retention factor of 10% was applied
   - Product amount applied (g): 20

External applied dose (mg/kg-bw): $1.41 \times 10^{-3}$ – 0.141

4. Hair dye

   Scenario: hair dye

   Assumptions
   - Essential oil concentration (%): 0.3–1
   - Exposure frequency (times/year): 10
   - Exposed area ($cm^2$): 637 (Health Canada 1995)
   - Retention factor of 10% was applied
   - Product amount applied (g): 100

   External applied dose (mg/kg-bw): $2.12 \times 10^{-2}$– 0.0705

5. Tanning preparation

   Scenario: sunscreen lotion

   Assumptions
   - Essential oil concentration (%): <0.1–0.1
   - Exposure frequency (times/year): 75
   - Exposed area ($cm^2$): 1.69E4 (Health Canada 1995)
   - Product amount applied (g): 10

   External applied dose (mg/kg-bw): $7.05 \times 10^{-3}$

6. Bath products (oil, foam, salts)

   Scenario: bath preparation

   Assumptions
   - Essential oil concentration (%): 0.1–30
   - Exposure frequency (times/year): 104
   - Exposed area ($cm^2$): 1.63E4 (Health Canada 1995)
   - Retention factor of 0.1% was applied
   - Product amount applied (g): 1.69E4

   External applied dose (mg/kg-bw): $9.17 \times 10^{-6}$–$2.75 \times 10^{-4}$

## Appendix A-3. Estimates of adult exposure via the oral route

1. Lipstick

   Assumptions:
   Essential oil concentration range (%) = 0.1–1
   Exposure frequency (times/year): $1.46\times10^{3}$
   Exposure type: Direct intake (ConsExpo 2006)
   Amount product ingested (g): 0.01
   Body weight (kg): 70.9

   Estimated chronic exposure (mg/kg-bw per day): Chronic external oral dose calculated through amortization over a year = $2.82\times10^{-5}$–$2.82\times10^{-4}$

## Appendix A-4 Estimates of adult exposure via the inhalation route

1. Deodorant – foot mist (pump spray)

   Scenario: trigger spray

   Assumptions
   Essential oil concentration range (%)= 0.3–1
   Amount of product applied (g): 13.8
   Uptake fraction (%): 100
   Body weight (kg): 70.9 (Health Canada 1995)

   Estimated acute exposure (per application): Mean event concentration: 0.145–0.482 mg/$m^3$

2. Fragrance – perfume

   Scenario: Fragrance

   Assumptions
   Essential oil concentration range (%) = 0.1–30
   Amount of product applied (g): 0.43–0.64
   Uptake fraction (%): 100
   Body weight (kg): 70.9 (Health Canada 1995)

   Estimated acute exposure (per application): Mean event concentration: $1.1\times10^{-5}$–0.0033 mg/$m^3$

3. Hair spray

Scenario: hair spray

Assumptions
Essential oil concentration range = 0.1–0.3%
Amount of product applied: 0.6 g
Uptake fraction: 100%
Body weight 70.9 kg (Health Canada 1995)

Estimated acute exposure (per application): Mean event concentration: $6.91\times10^{-5}$ – $2.07\times10^{-4}$ mg/m$^3$

4. Hair detangler

Scenario: Hair detangler with trigger spray

Assumptions
Essential oil concentration range = < 0.1–0.1%
Amount of product applied: 0.6 g
Uptake fraction: 100%
Body weight 70.9 kg (Health Canada 1995)

Mean event concentration: $3.65\times10^{-6}$ mg/m$^3$

## Appendix A-5. Infant exposure estimates via the dermal route

1. Baby shampoo (chronic exposure)

Scenario: Hair shampoo

Assumptions
Essential oil concentration range = 0.3–1%
Exposure frequency (times/year): 260
Exposed area: 330 cm$^2$ (Health Canada 1995)
Retention factor of 10% was applied
Amount of product applied: 34.1 g
Chronic external applied dose: (mg/kg-bw per day): 0.0162–0.0539

2. Baby skin cleanser – body wash (chronic exposure)

Scenario: skin cleanser

Assumptions
Essential oil concentration range = 0.3–1%
Exposure frequency (times/year): 329

Exposed area: 3.02E3 $cm^2$ (Health Canada 1995)
Retention factor of 1% was applied
Amount of product applied: 4.5 g
Chronic external applied dose: (mg/kg-bw per day): $8.11x10^{-4}$–$2.7x10^{-3}$

3. Baby massage oil (acute exposure)

Scenario: massage oil

Assumptions
Essential oil concentration range (%): 0.3–1
Exposure frequency (times/year): 24
Exposed area: 3020 $cm^2$ (Health Canada 1995)
Amount of product applied (g): 1.48

Chronic external applied dose (mg/kg-bw per day): 0.0296–0.0987

## Appendix A-6. Toddler exposure estimates

1. Baby shampoo

   Scenario 365, chronic dermal exposure

   Assumptions
   - Essential oil concentration range (%): 0.3–1
   - Exposure frequency (times/year): 365
   - Exposed area: 435 $cm^2$ (Health Canada 1995)
   - Retention factor of 10% was applied
   - Amount of product applied: 45 g

   Chronic external applied dose: (mg/kg-bw per day): 0.0145–0.0483

2. Baby skin cleanser – body wash

   Scenario: Skin cleanser, chronic dermal exposure

   Assumptions
   - Essential oil concentration range (%): 0.3–1
   - Exposure frequency (times/year): 329
   - Exposed area: 4.91E3 $cm^2$ (Health Canada 1995)
   - Retention factor of 1% was applied
   - Amount of product applied (g): 7.32

   Chronic external applied dose: $6.38\times10^{-4}$ –$2.13\times10^{-3}$

3. Baby massage oil

   Scenario: massage oil, acute dermal exposure

   Assumptions
   - Essential oil concentration range (%): 0.3–1
   - Exposure frequency (times/year): 24
   - Exposed area: 4910 $cm^2$ (Health Canada 1995)
   - Amount of product applied (g): 2.4

   Chronic external applied dose (mg/kg-bw per day): 0.0232–0.0774

4. Kids hair detangler (inhalation route exposure)

Scenario: hair spray with trigger spray

Assumptions

Essential oil concentration range (%): 0.1–0.3
Amount of product applied (g): 0.6
Uptake fraction(%): 100
Body weight (kg): 15.5 (Health Canada 1995)

Estimated acute exposure (per application) Mean event concentration: $3.65\times10^{-6}$ – $1.1\times10^{-5}$ mg/m$^3$

# Appendix B. Consumer products

## 1. Room mister (upper-bounding estimates exposure, ConsExpo 4.1 (ConsExpo2006)

Assumptions
Essential oil concentration range = 0.3–1%
Uptake fraction: 100%
Inhalation Adapted from ConsExpo 4.1 Trigger spray (RIVM 2006)

Exposure to spray
- Exposure duration: 240 min (estimated)
- Room volume: 58 $m^3$ (US EPA 1986)
- Ventilation rate: 0.5 $h^{-1}$ (US EPA 1986)
- Mass generation rate: 0.75 g/sec (RIVM 2006)
- Spray duration: 3 min (US EPA 1986)
- Airborne fraction: 1 (RIVM 2006)
- Weight fraction of non-volatile: 0.1
- Density of non-volatile: 1.8 $g/cm^3$ (RIVM 2006)
- Room height: 2.5 m (estimated)
- Inhalation cut-off diameter: 15 μm (RIVM 2006)
- Inhalation rate = 16.2 $m^3$/day (Health Canada 1995)

Estimated exposure: Mean event concentration: $2.1\times10^{-4}$ – $6.99\times10^{-4}$ $mg/m^3$

## Appendix C. Summary of health effects information for sclareol

The following acronyms are used within the text that follows:
LD50 = median lethal dose
LOAEC/LOAEL = lowest-observed-adverse-effect concentration/level
LOEC/LOEL = lowest-observed-effect concentration/level
NOAEC/NOAEL = no-observed-adverse-effect concentration/level.

**Acute toxicity** [No acute inhalation studies identified]

Lowest oral $LD_{50}$ > 5000 mg/kg bw in rats (0/10 death) (RIFM 1979a,b cited in Bhatia 2008).

[No additional acute oral studies identified]
Lowest dermal $LD_{50}$ > 5000 mg/kg bw in rabbits (0/6 death) (RIFM 1979a,b cited in Bhatia 2008)

[No additional acute dermal studies identified]
[Additional acute studies: Malone et al. 1991]

**Short-term repeated-dose toxicity**
Oral LOEL = 8.8 mg/kg-bw per day, based on increase in mean kidney weight relative to brain weight in male rats, increase in mean heart and spleen weights relative to the brain weight in female, in a study of 10 male and 10 female rats that were administered sclareol at dose of 8.8 mg/kg-bw per day 7 days per week via oral intubation for 30 days. No gross or microscopic alterations were observed (RIFM 2006a; cited in Bhatia et al. 2008).

**No study was identified for the following endpoints**:
Subchronic toxicity , chronic toxicity/ carcinogenicity, developmental toxicity, reproductive toxicity

**Genotoxicity and related endpoints: *in vitro***

(a) Positive: Human leukemic cell line HL60, 20 µg/mL of sclareol, dose- and time-dependent DNA cleavage (Dimas et al. 1999).
(b) Positive: Human colon cancer HCT116 cell line, 100 µM sclareol induced DNA breaks as early as 4 hours after sclareol addition (Dimas et al. 2007).

Essential oils from clary sage (*Salvia sclarea*) containing sclareol:

(a) Gene mutation in bacteria: Negative: *Salmonella typhimurium* TA1535, TA1537, TA98 and TA100, with S9 (Zani et al. 1969).

(b) DNA damage: Negative: *Bacillus subtilis* strain PB 1652(*trpC2, metB10, lys3, rec*$^{+}$) and PB 1791 (*trpC2, metB10, recE4*), 10–30 µL of *Salvia sclarea* L. (Zani et al. 1969).

**Dermal Irritation**

(a) Irritating: In rabbit, 5000 mg/kg produced irritant effects after an occluded application for 24 hours (RIFM 1979a, 1979b; cited in Bhatia et al. 2008).
(b) Not irritating: In 3 albino rabbits, 3% sclareol in petrolatum or 3% sclareol in alcohol SDA, applied with patches to clipped skin (RIFM 1975c, 1975d).

**Experience with human exposure**

(a) Dermal Irritation
Not irritating: In 106 volunteers, 48-hour closed patch test with 10% in petrolatum on the backs of volunteers (RIFM 1979c, 1981, 1986; cited in Bhatia et al. 2008).
Not irritating: In 35 volunteers, with 3% in alcohol SDA 39C, 48 hours, semi-occlusive (HRIPT induction) (RIFM 1975a; cited in Belsito et al. 2008).
(b) Not irritating: In 39 volunteers, with 3% in petrolatum, 48 hours, semi-occlusive (HRIPT induction) (RIFM 1975b; cited in Belsito et al. 2008).

**Sensitization**

(a) Sensitizing: In 29 and 26 volunteers, with 10% in petrolatum, sample no. 78-97 (melting point 84–90$^{o}$C) produced 1/29 sensitization reactions, and produced 3/26 sensitization reactions on retesting (RIFM 1979c; cited in Bhatia et al. 2008).
(b) Not sensitizing: In 23 volunteers, with 10% in petrolatum, sample no. 80-91R (melting point 96–106) produced 0/23 sensitization reactions (RIFM 1981; cited in Bhatia et al. 2008).
(c) Not sensitizing: In 28 volunteers, with 10% in petrolatum, sample no. 1140-85 (melting point 98–101$^{o}$C) produced 0/28 sensitization reactions (RIFM 1986; cited in Bhatia et al. 2008).

**Acute neurotoxicity**

Transient neurological effects (decrease in spontaneous motor activity, a decrease in respiratory rate and a compensatory increase in respiratory depth) were observed in male Sprague-Dawley rats (group size unknown) that were exposed to 0, 100, 316, or 1000 mg/kg-bw via a single intraperitoneal (i.p.) injection (of sclareol in sterile 0.25% aqueous agar) (Malone et al. 1991).

**Acute neurotoxicity for analogue sclareol glycol**

LOEL= 5 mg/kg, based on decrease of locomotor activity observed in groups of 8 male albino mice (strains unknown) that were exposed to 0, 5, 25, 50 or 100 mg/kg via a

single i.p. injection. The locomotor activity was recorded at 5-minute intervals for 30 minutes after injection. Sclareol glycol stimulated the locomotor activity at 5, 25 and 50 mg/kg, but at 100 mg/kg, it decreased the locomotor activity by 30% compared to controls (Georgieva 1988).
[Other neurotoxicity studies: Georgieva 1987, 1989a, 1989b]

## Appendix D – Summary of (Q)SAR prediction results for sclareol

### Table D-1. (Q)SAR Predictions on carcinogenicity

| Model/Species | Male mice | Female mice | Male rat | Female rat | Rat | Mice | Rodent | Mammal |
|---|---|---|---|---|---|---|---|---|
| Model Applier | N | P | P | N | N | N | N | - |
| Multicase Casetox | N | N | N | N | - | - | - | - |
| TOPKAT | ND | P | IC* | ND | - | - | - | - |
| Derek | - | - | - | - | - | - | - | NR |

ND – Not in domain (the model indicates that the query chemical is outside of its applicability domain)
"-" No model available in QSAR suite
NR – Nothing to report
N – Negative
P – Positive
IC*– Inconclusive (unreliable prediction, based on user-defined model-specific criteria other than the models' applicability domain)

**Table D-2. (Q)SAR predictions on genotoxicity**

| Model/endpoints | Model Applier | Multicase Casetox | TOPKAT |
|---|---|---|---|
| chromosomal aberrations. | P | N | - |
| chromosomal aberrations - other rodent | P | - | - |
| chromosomal aberrations - rat | ND | - | - |
| micronucleus mice | N | N | - |
| micronucleus rodent | P | - | - |
| *Drosophila* | N | ND | - |
| *Drosophila heritable* translocations | N | - | - |
| *Drosophila* SLRL | N | - | - |
| mam. mutation | N | - | - |
| mam. mutation dominant lethal | N | - | - |
| UDS | N | ND | - |
| UDS human lymphocytes | ND | - | - |
| UDS rat hepatocytes | N | - | - |
| mouse lymphoma mut | N | ND | - |
| *S. cerevisiae* | N | - | - |
| Yeast | N | - | - |
| HGPRT | N | - | - |
| *E. coli* | N | - | - |
| *E coli* w | N | - | - |
| microbial | N | - | - |
| Salmonella | N | N | N |

MA – Model Applier
CT – Multicase Casetox
TK – TOPKAT
ND – Not in domain (the model indicates that the query chemical to be outside of its applicability domain)
"-" No model available in QSAR suite
N – Negative
P – Positive

**Table D-3. (Q)SAR predictions on developmental toxicity - Model Applier**

| Endpoint/ Species | Mice | Rabbit | Rat | Rodent |
|---|---|---|---|---|
| Retardation | ND | ND | N | N |
| Weight decrease | ND | ND | P | N |
| Fetal death | ND | ND | N | N |
| Post implantation loss | ND | ND | P | N |
| Pre implantation loss | ND | ND | N | N |
| Structural | ND | ND | N | N |
| Visceral | ND | ND | N | N |

ND – Not in domain (the model indicates that the query chemical is outside of its applicability domain)
N – Negative
P – Positive

### Table D-4 (Q)SAR Predictions on developmental toxicity - Multicase Casetox

| Endpoint/Species | Hamster | Mammal | Miscellaneous |
|---|---|---|---|
| Teratogenicity | - | N | N |
| Developmental | ND | - | - |

ND – Not in domain (the model indicates that the query chemical is outside of its applicability domain)
"-" No model available in QSAR suite
N – Negative

### Table D-5. (Q)SAR Predictions on reproductive toxicity - Model Applier

| Model/Endpoint | Female Mice | Female rat | Female rodent | Male mice | Male rat | Male rodent |
|---|---|---|---|---|---|---|
| Species | Mice | Rat | Rodent | Mice | Rat | Rodent |
| Repro | ND | ND | ND | ND | ND | ND |
| Sperm | - | - | - | ND | ND | ND |

ND – Not in domain (the model indicates that the query chemical is outside of its applicability domain)
"-" No model available in QSAR suite

### Table D-6. (Q)SAR Predictions on Reproductive Toxicity -Multicase Casetox

| Mice | Rat | Rabbit | Human |
|---|---|---|---|
| N | N | N | ND |

ND – not in domain (the model indicates that the query chemical is outside of its applicability domain)
"-" no model available in QSAR suite
N – Negative