
Safety Assessment of *Eucalyptus globulus* (Eucalyptus) - Derived Ingredients as Used in Cosmetics

Status: Draft Report for Panel Review
Release Date: November 10, 2017
Panel Meeting Date: December 4-5, 2017

The 2017 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.



Cosmetic
Ingredient
Review

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MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Date: November 10, 2017

Subject: Safety Assessment of *Eucalyptus globulus* (Eucalyptus)-Derived Ingredients As Used In Cosmetics

Attached is the draft report of *Eucalyptus globulus* (Eucalyptus)-derived ingredients as used in cosmetics. [Eucaly122017Rep]

In September 2017, the Scientific Literature Review was posted for public comment with a request for additional data, including clarification of the definition of Eucalyptus Globulus Leaf Oil, which states that the oil may be sourced from other *Eucalyptus* species [Eucalyptus Globulus Leaf Oil is the volatile oil obtained from the leaves of *Eucalyptus globulus* and other species of *Eucalyptus*].

The source for all of these ingredients is the leaf or leaf/twig of the plant. The reported functions of the *Eucalyptus globulus* (eucalyptus)-derived ingredients include abrasive, fragrance ingredient, and skin-conditioning agent (miscellaneous and occlusive). A letter has been sent to RIFM asking their intentions towards the safety assessment of the fragrance-only ingredients recited in this report: Eucalyptus Globulus Leaf/Twig Oil and Eucalyptus Globulus Leaf Water.

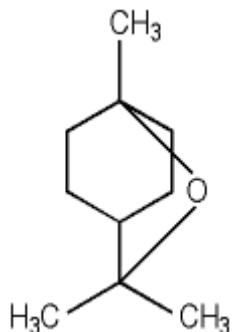
The Council has provided concentrations of use data and characterization of Eucalyptus Globulus Leaf Oil. [Eucaly122017Data_1-3] No other data have been provided. Council comments have been addressed. [Eucaly122017PCPC]

In most cases, the main component of Eucalyptus Globulus Leaf Oil is reported to be eucalyptol (54% to 95%; also called 1,8-cineole or cineole). Eucalyptol is a cosmetic ingredient that has not been reviewed by CIR. Should this ingredient be added to this safety assessment? To help the Panel make this decision, a summary of a sampling of toxicity and relevant data with regard to eucalyptol are provided with this memo.

If no further data are needed, the Panel should formulate a Discussion and issue a Tentative Report. However, if additional data are required, the Panel should be prepared to identify those needs and issue an Insufficient Data Announcement.

Eucalyptol (CAS No. 470-82-6)

Eucalyptol is the organic compound that conforms to the formula: (structure). It is the chief component of Eucalyptus Globulus Leaf Oil.¹



2017 VCRP Data²

05F - Shampoos (non-coloring)	EUCALYPTOL	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	EUCALYPTOL	1
08F - Nail Polish and Enamel Removers	EUCALYPTOL	1
09B - Mouthwashes and Breath Fresheners	EUCALYPTOL	12
12A - Cleansing	EUCALYPTOL	3
12C - Face and Neck (exc shave)	EUCALYPTOL	1
12J - Other Skin Care Preps	EUCALYPTOL	2
Total		22

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Eucalyptol undergoes oxidation in vivo with the formation of hydroxycineole which is excreted as glucuronide.³ In rats, 2-hydroxycineole, 3-hydroxycineole and 1,8-dihydroxycineol-9-oic acid were identified as main urinary metabolites. After oral administration to brushtail possums (*Trichosurus vulpecula*), p-cresol, 9-hydroxycineole, and cineol-9-oic acid were found in urine. Rabbits given eucalyptol by gavage excreted 2-exo- and 2-endo-hydroxycineole as well as 3-exo- and 3-endo-hydroxycineole in the urine.

Table 1. Overview of toxicity data on Eucalyptol.

Assay	Animal	Concentration	Results	Reference
Acute oral toxicity	Rats		LD50 = 2480 mg/kg	³
Acute oral toxicity	Rats		LD50 = 1560 mg/kg Lethal dose caused rapid cyanosis and stupor accompanied by irregular breathing, extreme sensitivity to noise, convulsions, and death from respiratory failure.	³
Acute oral toxicity	Mice	500 mg/kg	An increase in liver enzyme activity was also found in mice given 500 mg/kg orally.	³

Table 1. Overview of toxicity data on Eucalyptol.

Assay	Animal	Concentration	Results	Reference
Subacute Oral Toxicity - 28 days either by stomach tube (5 days/week) or in encapsulated form with the diet.	Fischer 344 rats (6/sex)	Stomach tube: 150, 300, 600 and 1200 mg/kg Encapsulated form in diet: 3750, 7500, 15,000 and 30,000 mg/kg, equivalent to 381 to 3342 mg/kg/day for males and 353 to 3516 mg/kg/day for females.	At dose levels of 600 mg/kg and higher, dose-related decrease of body weight gain and absence of a normal degree of hepatic centrilobular cytoplasmic vacuolization was observed in male rats. Other dose-related lesions in the liver, kidneys and parotid salivary glands were found at all dose levels in male rats fed encapsulated eucalyptol.	³
Subacute Oral Toxicity – administered by gavage for 28 days	Male Wistar rats (10)	0, 500, or 1000 mg/kg/day	There were decreases in terminal body weight and increased relative liver and kidney weights in both treatment groups. The relative brain weight was increased in 1000 mg/kg/day group. No macroscopic changes were observed. Only brain, liver and kidneys were examined histopathologically. No changes in the brain were observed; minor focal infiltration of mononuclear cells in liver was observed in all groups. In kidneys, a dose-related accumulation of eosinophilic protein droplets containing α 2u-globulin in the cytoplasm of proximal tubular epithelial cells was observed.	³
Subacute Oral Toxicity - 28 days either by stomach tube (5 days/week) or in encapsulated form with the diet.	B6C3F1 mice (6/sex)	Stomach tube: 150, 300, 600 and 1200 mg/kg Encapsulated form in diet: 3750, 7500, 15000 and 30000 mg/kg, equivalent to 600 to 5607 mg/kg/day for males and 705-6777 mg/kg/day for females.	The liver weight/body weight ratio in males was increased at all but the lowest dose given in encapsulated form as was the brain weight/body weight ratio in females at the top dose level. Microscopic examination revealed a minimal hypertrophy of centrilobular hepatocytes in mice of both sexes fed the encapsulated compound, especially at the two highest dose levels.	³
Chronic Oral Toxicity (and Carcinogenicity) – toothpaste administered by gavage (6 days/ week) for 80 weeks followed by 16 and 24 weeks rest.	Pathogen-free CFLP mice (52)	0, 8 and 32 mg/kg/day in 1 mL toothpaste base/kg/day	No treatment-related effects on body weights, feed consumption, survival, weight of adrenals, kidneys, liver, lungs or spleen, on the microscopic appearance of brain, lungs, liver and kidneys and on the tumor incidence were observed.	³
Genotoxicity – Ames assay	<i>Salmonella typhimurium</i> (TA98, TA100, TA1535, and TA1537)	Not specified	No mutagenic effects with or without metabolic activation	³
Genotoxicity – Ames assay	<i>S. typhimurium</i> (TA97a, TA98, TA100, and TA102)	Not specified	No mutagenic effects with or without metabolic activation	³
Genotoxicity – Chromosome aberration assay	Chinese hamster ovary cells	Not specified	No induced chromosome aberrations with or without metabolic activation	³
Genotoxicity – Sister chromatid exchange assay	Chinese hamster ovary cells	Not specified	Sister chromatid exchanges were induced in CHO cells only in the absence of metabolic activation at doses that induced cell cycle delay.	³
Genotoxicity – rec assay	<i>Bacillus subtilis</i>	Not specified	No evidence of DNA damage	³
Genotoxicity – rec assay	<i>Bacillus subtilis</i>	Not specified	No evidence of DNA damage	³
Dermal Irritation In Vitro - Episkin™	Human epidermis model	100%	Non-irritant. Relative mean viability of the treated tissue was 88.9% after 15 min exposure.	⁴
Dermal Irritation – Open mouse ear assay	Albino mice (10)	Not specified	Irritant dose in 50% of test individuals (ID_{50}) = 1.008 μ g/5 μ L (0.0202%)	⁵

Table 1. Overview of toxicity data on Eucalyptol.

Assay	Animal	Concentration	Results	Reference
Sensitization - local lymph node assay (LLNA)	Female mice (5)	25 % and 50 % v/v in acetone/olive oil 4:1, and 100 % v/v	Stimulation Index (SI): 25%, 1.43; 50%, 2.03; 100%, 5.08. The concentration of Eucalyptol expected to cause a 3-fold increase in 3HTdR incorporation (EC3 value) was calculated to be 65.90%. Eucalyptol was considered to be a sensitizer under the conditions of the test.	⁴
Ocular Irritation - In Vitro - Bovine Corneal Opacity and Permeability Assay	Bovine cornea	100%	Not considered to be an ocular corrosive or severe irritant	⁴

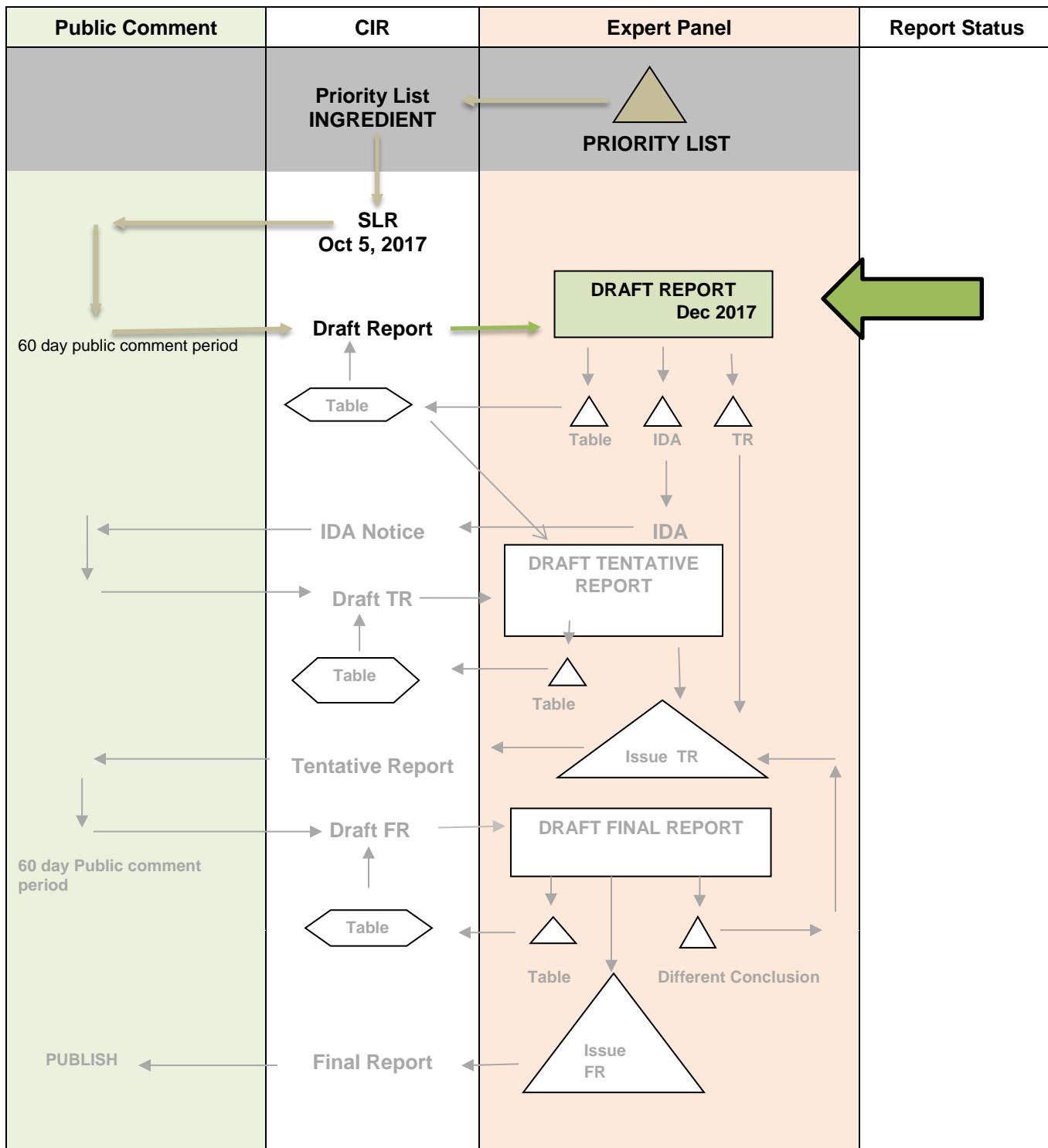
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SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Eucalyptus globulus* (Eucalyptus) -derived ingredients

MEETING Dec 2017



HISTORY – *Eucalyptus globulus*-Derived Ingredients

2016 – *Eucalyptus globulus* added to the priority list.

September, 2017 – SLR posted with the following data request:

The CIR is seeking, at a minimum, the following information on *Eucalyptus globulus*-derived cosmetic ingredients for use in the resulting safety assessment:

1. dermal irritation and sensitization data on *Eucalyptus globulus*-derived ingredients, for which such data were not available;
2. because these ingredients are botanicals and composition and extraction methods vary, specific chemical composition data, as well as the extraction solvent used for each cosmetic product being tested, should be included with all data that are submitted;
3. clarification of the definition of Eucalyptus Globulus Leaf Oil, which states that the oil may be sourced from other *Eucalyptus* species [Eucalyptus Globulus Leaf Oil is the volatile oil obtained from the leaves of *Eucalyptus globulus* and other species of *Eucalyptus*.]

December, 2017 – The Panel examines the Draft Report. Do we add Eucalyptol?

Eucalyptus globulus-Derived Ingredients

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	Web
Eucalyptus Globulus Leaf Oil	8000-48-4	Y	12/3	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	Y
Eucalyptus Globulus Leaf		Y	0	Y	Y	Y	Y	N	N	N	N	N	N	N	Y	Y	Y	Y
Eucalyptus Globulus Leaf Extract	84625-32-1	Y	0	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	Y
Eucalyptus Globulus Leaf Powder		Y	0	Y	Y	N	Y	N	N	N	N	N	N	N	N	N	N	Y
Eucalyptus Globulus Leaf/Twig Oil		Y	0	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	Y
Eucalyptus Globulus Leaf Water		Y	0	Y	Y	N	Y	n	N	N	N	N	N	N	N	N	N	Y

Botanical and/or Fragrance Websites (if applicable)

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	IFRA	RIFM
Eucalyptus Globulus Leaf Oil	8000-48-4	Y	N	N	N	N	N
Eucalyptus Globulus Leaf		Y	N	N	N	N	N
Eucalyptus Globulus Leaf Extract	84625-32-1	N	N	N	N	N	N
Eucalyptus Globulus Leaf Powder		N	N	N	N	N	N
Eucalyptus Globulus Leaf/Twig Oil		Y	N	N	N	N	N
Eucalyptus Globulus Leaf Water		N	N	N	N	N	N

Search Strategy

PUBMED

"Eucalyptus Globulus" OR "8000-48-4" OR "84625-32-1"

555 hits. Culled "AND tox*" - 48 (3 possibly useful); AND "geno*" - 0; AND repro* - 4 not useful; AND sensit* - 17 not useful; AND Irritat* - 0; AND carc* - 140 - 4 possibly useful.

SciFinder

"Eucalyptus Globulus", INCI names, and CAS Nos. 13 hits. None useful.

Safety Assessment of *Eucalyptus globulus* (Eucalyptus) - Derived Ingredients as Used in Cosmetics

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INTRODUCTION

This is a review of the safety of 6 *Eucalyptus globulus* (eucalyptus)-derived ingredients as used in cosmetics. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI Dictionary), the reported functions of the *Eucalyptus globulus* (eucalyptus)-derived ingredients listed below include abrasive, fragrance ingredient, and skin-conditioning agent (miscellaneous and occlusive; Table 1).¹ Eucalyptus Globulus Leaf/Twig Oil and Eucalyptus Globulus Leaf Water are reported to function only as fragrance ingredients.

Eucalyptus Globulus Leaf
Eucalyptus Globulus Leaf Extract
Eucalyptus Globulus Leaf Oil

Eucalyptus Globulus Leaf Powder
Eucalyptus Globulus Leaf/Twig Oil
Eucalyptus Globulus Leaf Water

Plant-derived cosmetic ingredients, such as *Eucalyptus globulus* (eucalyptus)-derived ingredients, may contain hundreds of constituents, some of which have the potential to cause toxic effects. For example, geraniol is reported to be a potential dermal sensitizer.²⁻⁶ In this safety assessment, the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) is reviewing information available to evaluate the potential toxicity of each of the *Eucalyptus globulus*-derived ingredients as whole, complex mixtures. Except for specific constituents of concern, CIR is not reviewing information that may be available to assess the potential toxicity of the individual constituents derived from *Eucalyptus globulus*.

The CIR Panel has reported on related ingredients that can be used to support the safety of the *Eucalyptus globulus* derived ingredients. Phytosterols were found in chloroform and methanol extracts of *Eucalyptus globulus* leaves.⁷ The Panel reviewed the safety of phytosterols, which are plant-derived sterols in 2013, and concluded that the phytosterols are safe as used.⁸

The names of the ingredients in this report are written in accordance with the International Nomenclature Cosmetic Ingredient (INCI) naming conventions, as shown above, capitalized without italics and without abbreviations. When referring to the plant from which these ingredients are derived, the standard taxonomic practice of using *italics* is followed (e.g., *Eucalyptus globulus*).

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (<http://www.cir-safety.org/supplemental/doc/preliminary-search-engines-and-websites>; <http://www.cir-safety.org/supplemental/doc/cir-report-format-outline>). Unpublished data are provided by the cosmetics and chemicals industries, as well as by other interested parties.

Pertinent data were discovered in reports prepared by other organizations, including reports by the European Chemicals Agency (ECHA),⁹ the International Program of Chemical Safety (INCHEM),¹⁰ the World Health Organization (WHO),¹¹ and the European Medicines Agency Products (EMA) Committee on Herbal Medicinal Products (HMPC).¹² Reports by these organizations are cited in this assessment to identify the source of the summary data obtained.

Often in the published literature, the information provided is not sufficient to determine how well the tested substance represents the cosmetic ingredient. Therefore, the taxonomic name is used or it is noted that the similarity could not be determined, unless it is clear that the test substance is similar to cosmetic ingredients. If the tested substance is a cosmetic ingredient, then the International Nomenclature of Cosmetic Ingredients (INCI) name is used.

CHEMISTRY

Definition and Structure

The definitions of the ingredients in this safety assessment are provided in Table 1. The genus *Eucalyptus* contains more than 750 species (i.e., *Eucalyptus cordata*, *Eucalyptus diversifolia*, *Eucalyptus gigantea*, *Eucalyptus glauca*, and *Eucalyptus pulverulenta*) and the term "eucalyptus" in the literature can refer to any or all of these.¹³ There are four subspecies of *Eucalyptus globulus*: bicostata, globulus, maidenii, and pseudoglobulus.¹⁴ It is not known if only one or all of these are used in cosmetics. This review cites studies where it can be reasonably certain that the test substance is *Eucalyptus globulus*. However, because the wINCI Dictionary defines Eucalyptus Globulus Leaf Oil as the volatile oil obtained from the leaves of *Eucalyptus globulus* and other species of *Eucalyptus*, data on other species may be included when deemed appropriate. "Eucalyptus oil" may be extracted from any *Eucalyptus* species that is rich in 1,8-cineole.¹¹ The other main species that *Eucalyptus* essential oil is extracted from are *Eucalyptus polybractea* and *Eucalyptus smithii*, which contain a minimum of 70% 1,8-cineole.¹⁵

In addition, according to the wINCI Dictionary, the CAS number that is associated with Eucalyptus Globulus Leaf Oil (defined above) is 8000-48-4. However, according to the Chemical Abstracts Service (CAS) database, the substance associated with CAS number 8000-48-4 is defined as "extractives and their physically modified derivatives of *Eucalyptus*, Myrtaceae." Also, according to the wINCI Dictionary, CAS number 84625-32-1 is associated with Eucalyptus Globulus Leaf Extract, which is defined as the extract of the leaves of *Eucalyptus globulus*. However, according to the CAS database, the substance associated with this CAS number is defined as "extractives and their physically modified derivatives such as

tinctures, concretes, absolutes, essential oils, oleoresins, terpenes, terpene-free fractions, distillates, residues, etc., obtained from *Eucalyptus globulus*, Myrtaceae.”

Plant Identification

Eucalyptus globulus, also referred to as blue gum or Tasmanian blue gum tree, is a member of the Myrtaceae family. These plants are evergreens that are indigenous to Tasmania and southeastern Australia, and are cultivated in subtropical regions of the world including Africa, South America, Asia, southern Europe (Spain and the Black Sea region) and the U.S.^{11,12}

Eucalyptus globulus is a large tree with smooth, very pale or ash-grey bark, which grows up to 3 to 20 m high.^{11,12,16,17,17-20} The bark types vary with plant age, and include: stringy bark, ironbark, tessellated bark, box, and ribbon. The bark cells are able to photosynthesize in the absence of foliage, giving the plant an increased ability to re-fix internal carbon dioxide following partial defoliation. This allows the tree to grow in less-than-ideal climates. Branchlets are quadrangular or glaucous. Eucalyptus leaves are ensiform (shaped like a sword blade; long and narrow with sharp edges and a pointed tip), usually ranging from 15 to 30 cm, and possibly up to 40 cm, long and 5 cm wide. The leaves, which are bluish-green in hue, alternate and are vertical. The leaves are studded with brown lenticels and colorless glands containing fragrant volatile oil. Younger leaves tend to have higher oil content than mature ones; however, 1,8-cineole content is higher in mature leaves. The flowers, which are present most of the year, have very short pedicels, mostly umbellate, sometimes 2 to 3 in a fascicle. The flowers consist of several white fluffy stamens (12 mm long), which are numerous, threadlike, white anthers opening in broad slits with round gland. The fruit has numerous small seeds and is enclosed by a cup shaped receptacle. The root system grows rapidly and uses large quantities of water; it consists of a strong taproot, at least 6 ft (1.8 m) and lateral roots that can spread up to 100 ft (30.5 m).

Physical and Chemical Properties

Physical and chemical properties are presented in Table 2. The odor of rectified Eucalyptus Globulus Leaf Oil changes over time as it is exposed to air.²¹ In the first 15 min, the odor is described as terpene-like, harsh, and conifer-like. At 15 min to 1 h, the odor is fresh, characteristic of 1,8-cineole, minty, and camphoraceous. At 2 to 8 h, the odor is hay- and cumin-like, similar to rosemary. At 5 to 20 h, the odor is wood, dusty, and powdery.

The specific gravity of Eucalyptus Globulus Leaf Oil and Eucalyptus Globulus Leaf/Twig Oil increases as the cineole content increases (0.9005 to 0.930).²¹

Eucalyptus Globulus Leaf/Twig Oil

Eucalyptus Globulus Leaf/Twig Oil is a colorless or pale yellow liquid that darkens slightly on long storage.¹¹ The odor of *Eucalyptus globulus* leaves is aromatic and camphoric; the taste is aromatic, pungent, and bitter.

Eucalyptus Globulus Leaf Oil

The specific gravity of Eucalyptus Globulus Leaf Oil collected by steam distillation was 0.919 at 20°C.¹¹

Method of Manufacture

The definitions of several of the *Eucalyptus globulus*-derived ingredients in this safety assessment give insight into possible methods of manufacture. For example, the definition of Eucalyptus Globulus Leaf Water states that this ingredient is an aqueous solution of the steam distillate obtained from the leaves of *Eucalyptus globulus*.¹

Methods of manufacture from the literature of Eucalyptus Globulus Leaf Oil and Eucalyptus Globulus Leaf Extract are presented in Table 3.

Composition/Constituents

The reference substances that are used to identify the legal entity composition of Eucalyptus Globulus Leaf Extract, Eucalyptus Globulus Leaf Oil, and/or Eucalyptus Globulus Leaf/Twig Oil in Europe were reported by ECHA (Table 4).⁹ The constituents in these ingredients include 1,8-cineole, pin-2(10)-ene, dipentene, and (R)-*p*-mentha-1,8-diene. 1,8-Cineole, the most common ingredient with the highest concentration, is shown in Figure 1.

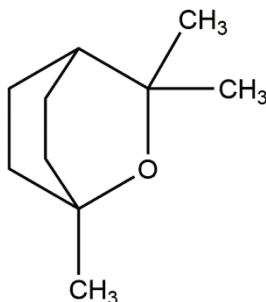


Figure 1. Reported primary component of *Eucalyptus*, eucalyptol (1,8-cineole)

Reported concentrations of *Eucalyptus globulus* essential oil and its constituents vary in the literature. *Eucalyptus globulus* leaves contain not less than 2% (v/w) essential oil, consisting of not less than 70% (w/w) 1,8-cineole (also known as cineol, cineole, or eucalyptol).¹¹ Another report states that fresh leaves of *Eucalyptus globulus* contained 54% to 61% 1,8-cineole, 19.5% to 24.3% α-pinene, 6.7% to 9.1% limonene, 2.1% to 5.4% α-terpinyl acetate, and 3.6% to 7.7% sesquiterpenes.¹² The author attributed the differences observed among the different preparation methods to potential hydrolyses during steam distillation. Another author reported that fresh leaves of *Eucalyptus globulus* contain only 1.87% volatile oil with 35.7% 1,8-cineole.¹²

Phytosterols were found in chloroform and methanol extracts of *Eucalyptus globulus* leaves but not in petroleum ether or aqueous extracts.⁷ Table 5 shows the major constituent groups found by using different extract mediums.

Eucalyptus Globulus Leaf Oil

The ranges of the constituents of Eucalyptus Globulus Leaf Oil (essential oil) are listed in Table 6. The main component of Eucalyptus Globulus Leaf Oil is 1,8-cineole. As shown in Table 7, gas chromatography-mass spectrometry (GC-MS) analyses demonstrates the variation in constituents of Eucalyptus Globulus Leaf Oil collected by steam distillation with geographic source location.^{20,22,23}

A supplier reported the constituents of Eucalyptus Globulus Leaf Oil, which included 1,8-cineole at 78.8% (Table 8).

Eucalyptus Globulus Leaf/Twig Oil

In general, the major constituent of Eucalyptus Globulus Leaf/Twig Oil is 1,8-cineole (54% to 95%).¹¹ In addition, there are moderate amounts of α-pinene (2.6%), *p*-cymene (2.7%), aromadendrene, cuminaldehyde, globulol and pinocarveol. Eucalyptus Globulus Leaf/Twig Oil for medicinal use contains not less than 70% (w/w) 1,8-cineole. Eucalyptus Globulus Leaf/Twig Oil also contains monoterpenes such as cymene, α-pinene, β-pinene, limonene, geraniol and camphene.¹²

Constituents of Concern

Constituents of concern are listed in Table 9. These include geraniol, a potential sensitizer, and quercetin, which is potentially genotoxic.^{2-6,24,25}

The International Fragrance Association (IFRA) publishes restrictions for fragrance ingredients. Constituents of *Eucalyptus globulus* leaves and oil that have restrictions established by the International Fragrance Association Standards are listed in Table 10.

Impurities/Constituents

No published impurities data were discovered and no unpublished data were submitted.

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetic industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentration by product category.

According to VCRP survey data received in 2017, Eucalyptus Globulus Leaf Oil is reported to be used in 414 formulations (208 leave-on formulations, 151 rinse-off formulations, and 55 formulations that are diluted for the bath).²⁶ Eucalyptus Globulus Leaf Extract is reported to be used in 73 formulations and Eucalyptus Globulus Leaf Powder is reported to be used in 2 formulations. The VCRP included an ingredient with the non-INCI name "Eucalyptus" with 41 reported uses (Table 11).

The results of the concentration of use survey conducted by the Council in 2017 indicate Eucalyptus Globulus Leaf Oil has the highest reported maximum concentration of use; it is used at up to 5.5% in body and hand products.²⁷ The rest of these ingredients with reported concentrations of use are used at 1.4% or less.

In some cases, no uses were reported in the VCRP, but concentration of use data were received from industry. For instance, Eucalyptus Globulus Leaf had no reported uses in the VCRP, but a use concentration in a skin cleansing formulation was provided in the industry survey. Therefore, it should be presumed there is at least one use in every category for which a concentration is reported.

There were no uses reported to the VCRP or industry survey for Eucalyptus Globulus Leaf/Twig Oil.

Eucalyptus Globulus Leaf Oil and Eucalyptus Globulus Leaf Extract are reported to be used in products that are used near the eyes (e.g., eye lotions at up to 0.038% Eucalyptus Globulus Leaf Oil), that may be ingested and come in contact with mucus membranes (e.g., mouthwashes and breath fresheners at up to 0.74% Eucalyptus Globulus Leaf Oil), and in baby products (e.g., lotions, oils, powders, and creams at up to 0.00067% Eucalyptus Globulus Leaf Oil).

Additionally, some of the *Eucalyptus globulus*-derived ingredients are used in cosmetic sprays and could possibly be inhaled; for example, Eucalyptus Globulus Leaf Oil is reported to be used in fragrance products at up to 0.4% and hair sprays at up to 0.002%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.^{28,29} Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.^{30,31}

The FDA lists “Eucalyptus globulus” as a non-traditional preservative for cosmetics in its Compliance Program Guidance Manual.³²

None of the *Eucalyptus globulus*-derived ingredients named in the report are restricted from use in any way under the rules governing cosmetic products in the European Union.³³

Non-Cosmetic

Eucalyptus globulus leaves are food additives for direct addition to food for human consumption and as a flavoring agent. [21 CFR 172.510]

Eucalyptus globulus oil may be used in over-the-counter (OTC) smoking deterrents. [21 CFR 310.544] *Eucalyptus globulus* oil may be used in OTC products that treat nasal decongestant (in a lozenge or mouthwash); sinusitis; dermal irritation; fever blisters/cold sores; and poison ivy, oak and sumac, and in astringent drug products. However, based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses. [21 CFR 310.545] *Eucalyptus globulus* oil may be used in the manufacture of denatured alcohol, rum, and other denatured spirits. [27 CFR 21.65; 27 CFR 21.151]

As a chemical residue in food, an exemption from the requirement of tolerance is established for residues of *Eucalyptus globulus* oil in or on honey, honeycomb, and honeycomb with honey when used at 2g or less *Eucalyptus globulus* oil per hive, where the eucalyptus oil contains 80% or more eucalyptol. [40 CFR 180.1271]

Eucalyptus globulus oil is permitted in combinations containing a nasal decongestant and an analgesic-antipyretic with a warning: Stop use and ask a doctor if pain or nasal congestion gets worse or lasts more than 5 days (children) or 7 days (adults), fever gets worse or lasts more than 3 days, redness or swelling is present, or new symptoms occur. [21 CFR 341.40]

For permitted combinations containing camphor, menthol, and *Eucalyptus globulus* oil, the labeling for antitussive ingredients should be used. [21 CFR 341.85]

Eucalyptus globulus leaf/twig oil is used orally to treat catarrh and coughs, and dermally as a rubefacient for treatment of rheumatic complaints in traditional medicine.¹¹ Other traditional medicinal uses that are not supported by experimentation or clinical data are treatment of cystitis, diabetes, gastritis, kidney disease (unspecified), neuralgia, laryngitis, leucorrhoea, malaria, pimples, ringworm, sinusitis, wounds, ulcers of the skin, urethritis and vaginitis.

Daily oral dosages range from 0.3 to 0.6 mL essential oil or equivalent preparations.¹¹ For example: one capsule of 100 to 200 mg, 2 to 5 times daily; one lozenge of 0.2 to 15.0 mg dissolved slowly in the mouth, every 30 to 60 min; or mouthwash as 20 mL of a 0.91mg/mL solution, gargled twice daily. Dosing by inhalation include 12 drops / 150 mL boiling water. For dermal use, daily dosage consists of several drops or 30 mL of the essential oil in 500 mL lukewarm water rubbed into the skin; 5% to 20% of the essential oil in liquid and semisolid preparations; or 5% to 10% in hydroalcoholic preparations. Since there are no sufficient clinical data on children, the EMA states that oral use should be restricted to adolescents over 12 years of age and the cutaneous use should be limited to children over 4 years of age.¹²

It is recommended that the maximum adult daily oral dose is 600 mg and the maximum dermal use level is 20%.⁶ The authors note that essential oils high in 1,8-cineole can cause central nervous system (CNS) and breathing problems in young children and recommend that the essential oil not be applied to or near the face of infants or children under ten years of age.

In the U.S., except for as a source of pollen for honey bees, *Eucalyptus globulus* is not generally used for human food, but as an additive.¹⁷ Australian Aborigines use the roots as a source of water, and cook and eat the roots. Dried *Eucalyptus globulus* leaves are fed to horses, cattle, and sheep.

The European Commission Scientific Committee on Food (SCF) concluded that the available toxicological studies

of 1,8-cineole are limited and inadequate to derive an acceptable daily intake (ADI).³⁴

TOXICOKINETIC STUDIES

Obtaining data on the toxicokinetics of unknown, complex mixtures would be impractical in practice, as is the case with many botanical ingredients. However, if the compositions are well understood, including the concentrations of constituents, such studies may be useful.

Dermal Penetration

Data on dermal penetration were neither found in the public literature, nor were such data submitted.

Penetration Enhancement

In Vitro

In vitro dermal penetration enhancement studies of Eucalyptus Globulus Leaf Oil and/or Eucalyptus Globulus Leaf/Twig Oil are summarized in [Table 12](#).

Generally, dermal penetration of chlorhexidine (CHG) increased in a concentration-dependent manner with Eucalyptus Globulus Leaf Oil through human skin samples over 24 h.³⁵ Eucalyptus Globulus Leaf Oil (82.9% cineole) at 5% facilitated greater CHG skin penetration to the deeper layers of the skin (below 300 µm) and 10% (v/v) Eucalyptus Globulus Leaf Oil enhanced CHG skin penetration in the upper 900 µm. CHG, with and without 50% Eucalyptus Globulus Leaf Oil, was detected at negligible levels in the receptor compartment over 24 h, suggesting that CHG did not permeate through the full skin thickness, and was retained within the tissue.

When the dermal penetration enhancement of Eucalyptus Globulus Leaf Oil (2.5%, 5%, or 7.5%) was tested with 2,3,5,6-tetramethylpyrazine (TMP), the enhancement ratios (ER) were 3.38, 4.47, and 4.64, respectively, for human skin.³⁶ The TMP flux across the human chest skin with 5% Eucalyptus Globulus Leaf Oil was 17-fold greater (346.0 mg/cm²/h) than the flux (20.1 mg/cm²/h) of a saturated solution of TMP without the oil. The receptor fluid was water. When the ability of Eucalyptus Globulus Leaf Oil (80% to 85% cineol) to enhance the dermal penetration of ketorolac was evaluated using a dermal patch across abdominal rat skin, the ERs were 1.80, 3.04, and 3.68 for 5%, 7.5%, and 10%, respectively.³⁷ Eucalyptus Globulus Leaf Oil increased the dermal penetration of 5-fluorouracil (5-FU) through rat skin using 2-cell diffusion cells; the ERs ranged from 58.49 to 82.55, depending on temperature (100°C through 140°C).³⁸

Absorption, Distribution, Metabolism, and Excretion (ADME)

Human

ORAL EXPOSURE

Eucalyptus Globulus Leaf Oil is readily absorbed and is expected to increase in the presence of lipid substances such as milk.¹⁰ It is excreted via the lungs, urine, skin, and feces.

TOXICOLOGICAL STUDIES

Acute Dose Toxicity

ANIMAL

Dermal

Eucalyptus Globulus Leaf Oil

Eucalyptus Globulus Leaf Oil (5000 mg/kg) was dermally administered to rabbits (n = 10) in a single dose. The rabbits were observed for 14 days.⁹ There were no mortalities or signs of toxicity. The dermal LD₅₀ was > 5000 mg/kg.

Oral

Eucalyptus Globulus Leaf Oil

Eucalyptus Globulus Leaf Oil (2200, 2900, 3700, or 6200 mg/kg in olive oil) was administered to fasted male ddY mice (n = 10) by gavage.⁹ The mice were observed for 7 days after dosing. There was no control group. Mortalities were 10%, 20%, 70%, and 100% at 2200, 2900, 3700, or 6200 mg/kg, respectively. The surviving mice had reduced growth. The oral LD₅₀ was 3320 (confidence interval 2770 to 3980) mg/kg Eucalyptus Globulus Leaf Oil in male mice.

Female albino Swiss mice (n = 6) were administered an aqueous emulsion comprising 5% Eucalyptus Globulus Leaf Oil (with polysorbate-80 (2%) as an emulsifier; 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 3.5 mL/kg) by gavage.³⁹ The control group were administered the vehicle (2% polysorbate-80 and water). The mice were fasted for 4 h prior to dosing and 2 h after dosing. The mice were observed every 30 min for 4 h, then daily for 14 days. The mice were then weighed, killed, and necropsied. There were no signs of toxicity or mortality in the mice in groups administered up to 2.0 mL/kg. At doses at and above 2.5 mL/kg, toxic effects were observed: restlessness immediately after administration followed by debilitation, reduced feed and water consumption, and gathering together and piloerection. The clinical signs disappeared in surviving mice, mostly after a day. In the 3.0 and 3.5 mL/kg groups, 1 of 6 and 4 of 6 mice died within 24 h of dosing, respectively. Necropsy revealed no noticeable changes in the appearance of the observed internal organs (stomach, liver, and kidney) in all treatment groups. The LD₅₀ of the emulsion was between 3 and 3.5 mL/kg.

SPF Sprague-Dawley (SD) rats ($n = 5/\text{sex}$) were administered Eucalyptus Globulus Leaf Oil (0, 2772, 3267, 3960, 4752, and 5742 mg/kg in water with polysorbate-80 and span-80 as emulsifiers) by gavage.⁴⁰ In the 5742 mg/kg group, at 50 min after dosing, the rats appeared to move slowly, gather together, have extreme sensitivity to noise, and have convulsions. The rats in the other treatment groups showed milder symptoms. The numbers of rats that died after dosing with 0, 2772, 3267, 3960, 4752, and 5742 mg/kg were 0, 1, 3, 6, 8, and 9, respectively. At necropsy of the rats that died, large amounts of undigested feed and Eucalyptus Globulus Leaf Oil was observed in stomach, and no tissue damage was observed except in the lungs and liver (details of the damage was not provided). The LD₅₀ was 3811.5 mg/kg (confidence interval: 3326.4 and 4306.5 mg/kg).

Male albino Wistar rats ($n = 10$) were administered Eucalyptus Globulus Leaf Oil (500, 1000, 1,500, 2,000, or 2,500 mg/kg; method of manufacture is presented in Table 3) by gavage.⁴¹ Mortality was determined after 24 h. The LD₅₀ was 2334.3 mg/kg and the LD₉₅ was 7632.13 mg/kg.

Eucalyptus Globulus Leaf Oil (concentrations not provided; in physiological saline) was administered to rats ($n = 5$) by gavage.⁹ The rats that were near death could not feed themselves. The oral LD₅₀ was 4400 mg/kg.

Inhalation

Eucalyptus Globulus Leaf Oil and Eucalyptus Globulus Leaf/Twig Oil

Male and female rabbits ($n = 8$ to 14) were lightly anesthetized and cannulated through the trachea.⁴² A second collecting tube was also installed. Steam from a boiling water bath, mixed with ambient air and cooled to the body temperature of the rabbits, was inhaled directly into the rabbit's trachea. Respiratory tract fluid was collected for a control period of 2 to 4 h. The collecting tracheal tube was then replaced by a new empty tube, and *Eucalyptus globulus* oil (0.4, 0.5, 1.0, 1.5, 3.0, 4.0, 6.0, 7.5, 9.0, 27, 81, 243, 729, 2187, 6561, and 19,683 mg/kg in ethyl alcohol; not known if leaf or leaf/twig oil) was added to the boiling water bath; respiratory tract fluid was collected for a subsequent 4 to 6 h or until the rabbit died. The highest dose caused deaths and significantly augmented the output of respiratory tract fluid; lower doses had no effect on the volume of respiratory tract fluid. Doses of 729 to 19,683 mg/kg produced increasingly lower values for the specific gravity of collected respiratory tract fluid and the two highest doses augmented the concentration of total solids and insoluble mucus. Doses which are considered to be in the therapeutic range for humans (3 to 243 mg/kg) were repeated in 2 successive years and in each instance they again produced no significant change in any parameter measured. Local irritation of the respiratory tract appeared after administration of the two highest doses.

HUMAN

Oral

Eucalyptus Globulus Leaf Oil

The literature on the oral toxicity in humans of Eucalyptus Globulus Leaf Oil is generally old (yrs 1900 – 1965). The following is a summary of this information. The substances are referred to as eucalyptus, eucalyptus oil, and similar names with little or no information on source plant parts, method of manufacture, or concentration/purity.

The probable oral lethal dose for adult humans is 0.05 mL to 0.5 mL/kg.¹⁰ The oral ingestion of Eucalyptus Globulus Leaf Oil may initially result in a burning sensation in the mouth, vomiting, diarrhea and epigastric pain. Vomiting may be delayed for periods varying from minutes up to 4 h. Permanent sequelae following recovery from the acute phase have not been reported although symptoms such as drowsiness, ataxia, and fatigue may occasionally persist for 1 to 2 weeks. Those subjects who suffered severe gastric irritation who promptly vomited recovered better but almost all made an uneventful recovery within 24 h. Recovery may be interrupted or reversed by bronchopneumonia. Death has occurred from within 15 min to 15 h after ingestion. One patient died 40 h after taking the oil, relapsing after apparent recovery.

The CNS (e.g., loss of consciousness, hypoventilation, depression of reflexes and convulsions), the gastrointestinal system (e.g., abdominal pain, vomiting and diarrhea), and the respiratory system (respiratory depression, dyspnea, pneumonitis, and bronchospasm) can be affected by oral ingestion. Gastrointestinal effects are frequently the initial effects, although drowsiness may occur in a few min and coma within 10 min. Urinary tract symptoms are only occasionally mentioned and there is little evidence of direct nephrotoxicity following doses of up to 30 mL in an adult or older child. The subject may vomit while drowsy or unconscious and aspiration is a major risk. Tachycardia and a weak irregular pulse have been noted. Muscle weakness and ataxia may occur. Nephritis is rare but has been recorded. Both mydriasis and miosis (more commonly) have occurred. CNS depression or vomiting has been delayed up to 4 h. Recovery is often within 24 h.¹⁰

Inhalation

Eucalyptus Globulus Leaf Oil

The literature on the inhalation toxicity in humans of Eucalyptus Globulus Leaf Oil is scarce. The following is a summary of this information. The substances are referred to as eucalyptus, eucalyptus oil, and similar names with little or no information on source plant parts, method of manufacture, or concentration/purity.

Inhalation of eucalyptus oil either as liquid or aerosol may result in pneumonitis. Inhalation of vapor may be used medicinally and there are no data available on toxicity by this route.¹⁰ However, respiratory problems include bronchospasm, tachypnea, pulmonary edema, respiratory depression, and pneumonitis following aspiration of the oil. Eucalyptus oil inadvertently given intranasally has caused irritated nasal mucous membranes.

Short-Term Toxicity Studies

No published short-term dermal or inhalation toxicity studies were discovered and no unpublished data were submitted.

Oral

Eucalyptus Globulus Leaf Extract

An aqueous Eucalyptus Globulus Leaf Extract (2000 mg/kg/d; 0.2 mL; method of manufacture is presented in [Table 3](#)) was orally administered (dose not specified) to male Swiss albino mice ($n = 10$) for 10 days.⁴³ The mice in the control group were administered distilled water. The extract was made fresh daily.

There were no mortalities. The treated mice demonstrated general weakness and decrease in physical activity. The treated mice had loss of body fur, ruffled fur, and changes in their white coat color. The treated mice had reduced feed intake and lost weight (-13.35%); the control mice gained weight (1.65%). There was a statistically significant reduction in hemoglobin concentration (3.12%), packed cell volume (PCV; 3.11%), red blood cell count (RBC; 11.31%), and total white blood cell count (WBC; 20.97%), indicating severe leucopenia. The platelet count was also reduced (15.55%) compared with that in the control group. There were significant changes in enzymes demonstrating liver impairment: aspartate aminotransferase (AST), 33.0 ± 1.0 vs. 75.0 ± 1.0 international units (IU)/L, 127.27% increase and alanine aminotransferase (ALT) 35.0 ± 1.0 vs. 65.0 ± 1.0 IU/L, 85.71% increase. There was a significant increase in creatinine (0.09 ± 0.1 vs. 1.90 ± 0.1 mg/dL) and urea levels (75.0 ± 1.0 vs. 25.0 ± 1.0 mg/dL) in the treated mice, as compared to controls. Gross examination of the treated mice showed pale livers, congestion and hemorrhages in the lung of some of the mice, enlarged spleens, and mild congestion in heart in some of the mice. Histological examination of the treated mice showed damage to hepatic cells manifested by swollen hepatocytes with vacuolated cytoplasm, which was very extensive in some cells. Many necrotic cells with pyknotic or karyolytic nuclei were observed. Some of the central veins of the livers were congested and some hepatocytes had enlarged nuclei. There were no changes in the livers of the control group. There were no changes in the kidneys of the control group. Histological examination showed that renal tubules of the treated mice had mild to severe degeneration. The degenerative changes were in the tubular epithelium reflecting failure of membrane ion pumps, allowing the cell to accumulate fluid. Examination of the cerebrum of the control mice revealed no abnormalities. Administration of aqueous Eucalyptus Globulus Leaf Extract caused significant neurodegenerative changes including a decrease in size and number of neurons in the cerebral cortex. Many glial cells with dense fragmented nuclei were observed.⁴³

An aqueous Eucalyptus Globulus Leaf Extract (0, 80, 100, or 120 mg/kg; 1 mL) was administered by gavage to albino *Rattus norvegicus* rats ($n = 6$) for 7 days.⁴⁴ Homogenous aqueous suspensions of the extract (method of manufacture is presented in [Table 3](#)) were made before being administered to the rats. Controls were administered distilled water. The activities of acid phosphatase (ACP), alkaline phosphatase (ALP), superoxide dismutase (SOD) and the level of malondialdehyde (MDA) were determined in the liver and serum. ACP and ALP activities were significantly increased in the livers with no difference in their serum activities. Activity of SOD was significantly increased in the liver in the 100 and 120 mg/kg groups. There was a significant increase in the level of MDA in the liver of all treatment groups and in the serum of the 120 mg/kg group. The authors state the results indicate that the aqueous Eucalyptus Globulus Leaf Extract may have deleterious effects on liver membrane structure and functional integrity.

In a combined repeated dose and reproduction/developmental study, Eucalyptus Globulus Leaf Extract (0, 100, 300, or 1000 mg/mL; 4 mL/kg in corn oil) was administered by gavage to Crl:CD(SD) rats ($n = 10/\text{sex}$).⁹ The study was conducted in accordance with Organisation for Economic Co-operation and Development (OECD) Guideline (GL) 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test). The males were treated starting from 2 weeks before mating for at least 5 weeks. The females were treated from 2 weeks before mating until lactation day 6. The rats were killed and necropsied. [For results related to reproduction and development, see [DEVELOPMENTAL AND REPRODUCTIVE TOXICITY \(DART\) STUDIES](#)]

One female in the 1000 mg/kg/day group was found dead on Day 15 after mating, which was not attributed to treatment. During the first week of dosing, both males and females in the 1000 mg/kg/day group displayed transient signs of reduced activity and unsteady muscle reactions. Rats in the 1000 mg/kg/day group also displayed chin rubbing and salivation; salivation was also recorded in females in the 300 mg/kg/day group. Detailed physical and arena observations, sensory reactivity, grip strength or motor activity assessments of the animals did not detect any changes attributed to the test substance. Bodyweight gain of males in the 1000 mg/kg/day group was low during week 1. During gestation, bodyweight gain and feed consumption was low in females in the 1000 mg/kg/day group. Feed consumption remained low for females in the 1000 mg/kg/day group during lactation.

Changes in hematology parameters were not considered to be adverse at the level observed. Biochemical analysis of blood plasma during week 2 of dosing showed high alanine amino transferase activity and bile acid concentration in females in the 1000 mg/kg/day group. Urea concentration was high and triglyceride concentration was low in males in the 1000 mg/kg/day group. The authors stated that these changes may be associated with the microscopic changes to the liver and kidneys. Male rats at all doses had hyaline droplet nephropathy in the kidneys, accompanied by tubular casts and/or tubular degeneration/regeneration. Hyaline droplet nephropathy in the kidneys of male rats is caused by accumulation of α 2 microglobulin (produced by the liver) in the proximal tubules, which leads to subsequent damage and regeneration of the tubular epithelium. The authors note that this has been reported with a number of organic chemicals, but it appears to be a

male, rat-specific toxicological response that has no counterpart in humans. The absence of any tubular injury in the test article treated females supports the conclusion that the tubular degeneration is secondary to the male specific hyaline droplet accumulation.

All dose levels resulted in centrilobular hepatocytic hypertrophy in the livers of males and an increase in glycogenic vacuolation in the livers of females. Minimal centrilobular hepatocytic hypertrophy of the male livers associated with liver weight increase was considered an adaptive change likely associated with microsomal enzyme induction. A slight increase in the incidence and severity of glycogenic vacuolation in the livers of treated female compared with controls may be partially responsible for the liver weight increase. Although centrilobular hepatocytic hypertrophy was not recorded in the females, a minimal diffuse hypertrophy could account for the liver weight increase in this sex, but would be difficult to detect histologically. The liver changes were not considered to be adverse. There were no microscopic correlates for the decrease in spleen weight and the increase in adrenal weight of the high-dose females.

The no-observed-adverse-effect-level (NOAEL) for males was 1000 mg/kg based on hyaline droplet nephropathy at all dose levels; however this response is considered to be rat specific and to have no counterpart in man. The NOAEL for females was 300 mg/kg based on effects on bodyweight, feed consumption.⁹

Male Wistar rats (n = 8) were administered Eucalyptus Globulus Leaf Extract (130 mg/dry leaves/kg) in drinking water for 42 days.⁴⁵ A control group was administered water. The extract (method of manufacture is presented in Table 3) was mixed with water (1 g/L) and provided to the rats as their drinking water. There were no differences in creatinine, urea, protein, or uric acid in the blood of the two groups. In measurements of oxidative damage and antioxidant activities in the kidneys, there were no differences in levels of peroxidation and activities, SOD, glutathione peroxidase (GPX), and catalase (CAT). There were no differences observed between the two groups when the kidneys were examined microscopically.

Eucalyptus Globulus Leaf Oil

Female albino Swiss mice (n = 12/sex) were administered Eucalyptus Globulus Leaf Oil (0, 1.5, or 2.0 mL/kg) by gavage for 84 days (12 weeks).³⁹ The control group were administered the vehicle (2% polysorbate-80 and water). After the last dose, blood samples were collected. The mice were killed and the livers and kidneys examined. There were no signs of toxicity and no mortalities for either treatment group. Body weights were similar between the treatment and control groups. There were no significant changes in hematological parameters in either treatment group compared to the control group. The general microscopic architecture of the liver sections of mice in the 1.5mL/kg group was similar to controls. Some areas of the liver sections of mice in the 2.0 mL/kg group showed that the general hepatolobular architecture was altered in that pyknosis, clear spaces in the cytoplasm (vacuolations) of hepatocytes, and focal necrosis were observed. Kidney sections of mice in the 1.5 mL/kg group showed no significant structural differences. Pyknosis of renal tubular epithelial cells and widening of tubular lumen was observed in sections of kidneys of mice in the 2.0 mL/kg group. Hyaline casts in renal tubules and perivascular lymphocytic infiltrations were also observed in small areas of kidney sections in the 2.0mL/kg group.

Eucalyptus Globulus Leaf Oil (100, 300, or 1000 mg/kg/day in corn oil) was administered to Crl:CD (SD) rats (n = 3/sex) for 2 weeks.⁹ There were no mortalities during the study. Clinical signs were salivation in isolated females in the 300 and 1000 mg/kg/day groups, which the authors considered minor and did not indicate an association with the test material. Other signs were transient bodyweight loss and low feed consumption in males in the 1000 mg/kg/day group during Days 1 to 5. Necropsy showed that liver and kidney weights increased with increasing dose level in males; in females, increased liver weights were only observed in females in the 1000 mg/kg/day group. Thickening of the mammary tissue was observed in 2 and 1 males in the 300 and 1000 mg/kg/day groups, respectively, and 1 female in the 1000 mg/kg/day group. Under the test conditions, the lowest-observed-adverse-effect-level (LOAEL) and NOAEL in female rats could be considered as 300 and 100 mg/kg/day, respectively, based on the clinical signs at 300 and 1000 mg/kg/day and increased liver weight at 1000 mg/kg/day. Since dose-related increases in liver and kidney weights were observed in males at all doses, no NOAEL could be identified for the male rats in this study. The LOAEL in male rats could be considered as 100 mg/kg bw/day.

Male albino Wistar rats (n = 5/sex) were administered Eucalyptus Globulus Leaf Oil (0 or 233 mg/kg in corn oil; 1/10 LD₅₀; method of manufacture is presented in Table 3) by gavage every 3 days for 30 days.⁴¹ Blood samples were collected on Days 15 (5th dose) and 30 (10th dose). The rats were then killed and necropsied. There was a significant increase in WBC counts and a decrease in hemoglobin concentration and platelets count in both blood samples. RBC counts were below control levels at 10th dose. The activities of serum glutamic oxalacetic transaminase (SGOT) and glutamic pyruvic transaminase (SGPT) enzymes were significantly increased at both the 5th and 10th doses in treated rats. There were mild effects on kidney function in that there was a significant increase in creatinine and urea concentration at the 10th dose. Histopathological studies on liver and kidney revealed that Eucalyptus Globulus Leaf Oil caused relatively moderate pathological changes in the liver as congestion of the blood vessels in the portal area associated with inflammatory infiltration. There was also induced desquamation of the epithelial cells of the renal tubules.

SPF Sprague-Dawley (SD) rats (n = 5/sex) were administered Eucalyptus Globulus Leaf Oil (0, 396, 792, and 1188 mg/kg in water with polysorbate-80 and span-80 as emulsifiers) by gavage for 30 days.⁴⁰ There were no clinical signs during the experimental period. In male rats, the body weights of low-dose group (396 mg/kg) was higher than the control group; the body weights of the middle-dose group (792 mg/kg) and high-dose group (1188 mg/kg) were significantly lower than those of the control group. In female rats, the body weights of all of the experimental groups were lower compared to the control group. There were no differences in hematological parameters. Heart rates and respiratory rates were similar

between groups.

The serum biochemical parameters were similar between groups except that there were significant differences between the control group and the mid- and high-dose groups for: aspartate transaminase (increased), creatinine (increased), and glucose (decreased). There were no differences in organ weights between groups. In the livers of the experimental groups, the central venous extended with hyperemia and varying degrees of vacuolar degeneration of hepatocytes. In the spleens, red pulp extended with hyperemia and a large number of macrophages and Langerhans cells infiltration was observed in the mid- and high-dose groups. Glomeruli (with varying degrees of hyperemia), renal tubular epithelial cells with varying degrees of granular degeneration, and narrowed renal tubes were observed in the kidneys of the mid- and high-dose groups. Histological examination showed that there were no significant differences with regard to the heart, lung, stomach, intestines, testicles and ovaries.⁴⁰

Subchronic Toxicity Studies

No published subchronic toxicity studies were discovered and no unpublished data were submitted.

Chronic Toxicity Studies

No published chronic toxicity studies were discovered and no unpublished data were submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Oral

Eucalyptus Globulus Leaf Oil

In a combined repeated dose and reproduction/developmental study, Eucalyptus Globulus Leaf Oil (100, 300, or 1000 mg/mL; 4 mL/kg in corn oil) was administered by gavage to CrI:CD(SD) rats (n = 10/sex).⁹ The study was conducted in accordance with OECD GL 422. [For results related to short-term toxicity, see [Short-Term Toxicity Studies](#)]

There were no adverse effects detected in reproductive assessments on estrous cycles, mating performance and fertility, gestation length and parturition observations, and reproductive performance. There were no significant effects of the Eucalyptus Globulus Leaf Oil on litter size, offspring survival indices or sex ratio. The body weights of offspring at birth were similar to that of the control group. However, body weight gains of male and female offspring in the 1000 mg/kg/day group were low (approximately 27% to 28% lower than the control group), and by day 4 after parturition absolute body weights of this group were also significantly lower than that of the control group. At microscopic examination, there were no findings attributed to treatment for offspring examined before or at the end of the experiment. A slightly high incidence of cold to touch was observed in litters in the 1000 mg/kg/day group. Under the test condition, the NOAEL for the females was considered to be 300 mg/kg/day for systemic toxicity, based on lower body weight gain and feed consumption during gestation. The authors stated that both findings appeared to be associated with pregnancy status. It was not possible to link this effect to the taste of the substance since females had shown a significant duration of normal bodyweight and feed performance prior to Day 6 of gestation and after birth of the pups. These latter observations appeared to indicate recovery in females. The NOAEL for developmental toxicity was 300 mg/kg/day, which was based on lower offspring bodyweight gain, and clinical signs (pups cold to touch) that were only observed in the 1000 g/kg/day group. This effect may be associated with test material entering the milk. The authors note that fat soluble test materials have a higher chance of becoming incorporated in the milk and Eucalyptus Globulus Leaf Oil is fat soluble. A NOAEL at 300 mg/kg/d was determined for systemic effects in the offspring based on the magnitude of the weight reduction, which was quite high. The effects on offspring body weight were not selective and have been observed at a dose producing maternal toxicity, and therefore the substance was not considered to be a selective reproductive toxicant. The NOAEL for reproductive toxicity was 1000 mg/kg/day, since no adverse effects were observed.

GENOTOXICITY STUDIES

In Vitro

Genotoxicity studies are summarized in Table 13.

Eucalyptus Globulus Leaf Extract was not mutagenic, with and without metabolic activation, at up to 5000 µg/plate in an in vitro mammalian cell gene mutation test using mouse lymphoma cells.⁹

Eucalyptus Globulus Leaf Oil was not genotoxic in a bacterial reverse mutation assay using *Salmonella typhimurium* and *Escherichia coli* at up to 5000 µg/plate, with and without metabolic activation.⁹ Eucalyptus Globulus Leaf Oil was not genotoxic in an in vitro mammalian chromosome aberration test using human lymphocytes and an in vitro mammalian cell gene mutation test using mouse lymphoma L5178Y cells.⁹

Eucalyptus Globulus Leaf Oil at 0.12 and 0.25 µL/mL was found to increase the mitotic instability of the original diploid strain and the number of diploid mitotic recombinants of *Aspergillus nidulans*.¹² The genotoxicity of the oil was associated with the induction of mitotic crossing-over or with oil-broken chromosomes.

CARCINOGENICITY STUDIES

No published carcinogenicity studies were discovered and no unpublished data were submitted.

Tumor Promotion

Dermal

Eucalyptus Globulus Leaf Oil

Eucalyptus Globulus Leaf Oil (neat; 0.25 mL) was tested for tumor promotion in mice.⁴⁶ A single application of 9,10-dimethyl-1,2-benzanthracene (DMBA) was administered to the clipped backs of 8-week-old mice (n = 14). The dose of DMBA (225 µg; 2 mL in acetone) was described as being sufficient to initiate skin tumor formation but, generally, inadequate for complete carcinogenesis. After three weeks, Eucalyptus Globulus Leaf Oil was administered to the backs of the mice once per week for 33 weeks. Dorsal hair was removed as necessary. The control group (n = 13) received the DMBA treatment alone. Papillomas were observed on 4 of 14 mice in the treatment group and 0 of 13 in the control group.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Eucalyptus Globulus Leaf Oil (neat; 5000 mg/kg) was dermally administered to rabbits (n = 10) in a single dose. The rabbits were observed for 14 days.⁹ Slight erythema was observed in 5 of 10 rabbits, moderate erythema in 3 of 10 rabbits, and moderate edema in 10 of 10 rabbits. No further details were provided.

Sensitization

No published sensitization studies were discovered and no unpublished data were submitted. However, patch test studies of dermatologic patients were found; these studies are presented in Clinical Studies.

PHOTOSENSITIZATION/PHOTOTOXICITY

In Vitro

An in vitro photohemolysis test (human erythrocyte suspensions) was used to evaluate the phototoxicity of Eucalyptus Globulus Leaf Oil.⁴⁷ The UVA-rich light source was a UVASUN 5000 lamp (320 to 460 nm; 42 mW/cm²) and the UVB-rich light source was a lamp with TL 20 W/12 light bulbs (between 275 and 365 nm; 1 mW/cm² [UVB] and 0.4 mW/cm² [UVA]). There was no hemolysis observed under the test conditions. Therefore, the authors concluded that the test substance is not expected to be photosensitizing.

OCULAR IRRITATION STUDIES

In an eye irritation study performed in accordance with OECD GL 405 (acute eye irritation/corrosion), undiluted Eucalyptus Globulus Leaf Oil (0.1 mL) was instilled into the right eye of a single New Zealand White (Hsdlf:NZW) rabbit.⁹ After consideration of the ocular responses produced in the first treated animal, two additional animals were treated. The eyes were not rinsed after administration. The left eye of each rabbit served as control. Animals were observed 1, 24, 48 and 72 h after dosing under a light source from a standard ophthalmoscope. The reactions in the conjunctiva (redness, chemosis and discharge), the iris and the cornea (opacity and area involved) were scored according to the Draize scale. No corneal or iridial effects were observed during the study. Moderate conjunctival irritation was noted in all treated eyes 1 h after treatment with minimal conjunctival irritation noted at the 24- and 48-h observations. All treated eyes appeared normal at 72 h. Mean scores calculated for each rabbit over 24, 48 and 72 h were 0.0/0.0/0.0 for cornea opacity, 0.0/0.0/0.0 for iris lesions, 0.7/1.0/0.7 for redness of the conjunctivae, and 0.7/0.7/0.7 for chemosis. One rabbit had no body weight gain and two animals showed expected gain in body weight during the study.

CLINICAL STUDIES

Retrospective and Multicenter Studies

Retrospective and multicenter studies of Eucalyptus Globulus Leaf Oil are summarized in Table 14.

In a retrospective study of dermatologic patients during the years 2010 to 2015, 1 of 22 subjects was sensitized with Eucalyptus Globulus Leaf Oil.² In a retrospective study of dermatologic patients during the years 2000 to 2007, 4 of 679 (0.6%) had positive results in sensitization studies with Eucalyptus Globulus Leaf Oil (2%).⁴⁸ In patch tests of subjects (n = 96) with dermatitis and/or eczema, 5 subjects had positive reactions to Eucalyptus Globulus Leaf Oil (2% in petrolatum).⁴⁹ Two of the subjects were scored with a +/- reaction, 2 with a + reaction, and 1 with a ++ reaction. In a retrospective study of dermatologic patients during the years 2000 to 2009, of the 6680 subjects that were tested for sensitization to Eucalyptus Globulus Leaf Oil, 0.24% had positive reactions.⁵⁰ In a cross-sectional study conducted in Belgium (2000 to 2009) of 301 subjects having had reactions to fragrance mixes, a reaction was confirmed to "eucalyptus oil" in 1 of 23 bath and shower products and 1 in 88 skin care products.⁵¹ In sensitization tests (method not clear) of subjects (n = 200) in Poland with dermatitis, 3 subjects had positive reactions to Eucalyptus Globulus Leaf Oil (concentration not specified).⁵² When this study was continued on additional subjects (n = 450) with dermatitis, 5 subjects had a positive reaction to Eucalyptus Globulus Leaf Oil (concentration not specified).⁵³ In sensitization tests (method not clear) of subjects (n = 5315) in London with dermatitis, 1 subject had a positive reaction to Eucalyptus Globulus Leaf Oil (concentration not specified).⁵⁴

Case Reports

Case reports of adverse reactions to dermal, oral, and inhalation exposure to Eucalyptus Globulus Leaf Oil are presented in Table 15.

Dermal effects ranged from none to eczema, erythematous macular lesions, papules and vesicles, and/or pruritus.⁵⁵⁻⁶⁰ Oral effects included esophageal pain, gasping for breath, restlessness, dyspnea, weak pulse, vomiting, drowsiness, and convulsions.^{10,59,61-64} Inhalation effects included strong characteristic smell on the breath, coughing, chest tightness, dyspnea, hoarseness, and wheezing.^{59,65} In children, effects included nasal and epigastric burning, nausea, vomiting, dizziness, muscular weakness, miosis, tachycardia, and a feeling of suffocation. Cyanosis, delirium, and convulsions may be exhibited, especially in infants.⁶⁶

SUMMARY

This is a review of the safety of 6 *Eucalyptus globulus*-derived ingredients as used in cosmetics. According to the wINCI Dictionary, the reported functions of the *Eucalyptus globulus*-derived ingredients include abrasive, fragrance ingredient, and skin-conditioning agent (miscellaneous and occlusive). Eucalyptus Globulus Leaf/Twig Oil and Eucalyptus Globulus Leaf Water are reported to function only as fragrance ingredients.

In most cases, the main component of Eucalyptus Globulus Leaf Oil is 1,8-cineole (54% to 95%). The other reported main components of Eucalyptus Globulus Leaf Oil include α -pinene (9.22% to 24.6%), globulol (0.819% to 2.817%), and β -pinene (0.217% to 1.237%), depending on the origin of the plant.

According to VCRP survey data received in 2017, Eucalyptus Globulus Oil is reported to be used in 414 formulations (208 leave-on formulations, 151 rinse-off formulations, and 55 formulations that are diluted for the bath). Eucalyptus Globulus Leaf Extract is reported to be used in 73 formulations and Eucalyptus Globulus Leaf Powder is reported to be used in 2 formulations. The VCRP included an ingredient with the non-INCI name "Eucalyptus" with 41 reported uses. The results of the concentration of use survey conducted by the Council in 2017 indicate Eucalyptus Globulus Leaf Oil has the highest reported maximum concentration of use; it is used at up to 5.5% in body and hand products. The rest of these ingredients with reported concentrations of use are used at 1.4% or less. There were no uses reported to the VCRP or industry survey for Eucalyptus Globulus Leaf/Twig Oil.

In vitro studies, Eucalyptus Globulus Leaf Oil has been shown to increase the dermal penetration of CHG, TMP, ketorolac, and 5-FU.

The dermal LD₅₀ was > 5000 mg/kg Eucalyptus Globulus Leaf Oil (the highest dose tested) in rabbits.

The oral LD₅₀ for Eucalyptus Globulus Leaf Oil was 3320 mg/kg in male mice. There were no signs of toxicity or mortality in the mice in groups administered up to 2.0 mL/kg Eucalyptus Globulus Leaf Oil. At doses at and above 2.5 mL/kg, toxic effects were observed; the clinical signs disappeared in surviving mice, mostly after a day. In the 3.0 and 3.5 mL/kg groups, 1 of 6 and 4 of 6 mice died within 24 h of dosing, respectively. Necropsy revealed no noticeable changes in the appearance of the observed internal organs (stomach, liver, and kidney) in all treatment groups.

In rats, the oral LD₅₀ for Eucalyptus Globulus Leaf Oil was reported as 3811.5 mg/kg in one study and 4400 mg/kg in another.

The probable oral lethal dose for adult humans is 0.05 mL to 0.5 mL/kg. The oral ingestion of Eucalyptus Globulus Leaf Oil may initially result in a burning sensation in the mouth, vomiting, diarrhea and epigastric pain. Vomiting may be delayed for periods varying from minutes up to 4 h. Permanent sequelae following recovery from the acute phase have not been reported although symptoms such as drowsiness, ataxia and fatigue may occasionally persist for 1 to 2 weeks. Those subjects who suffered severe gastric irritation who promptly vomited recovered better but almost all made an uneventful recovery within 24 h. Recovery may be interrupted or reversed by bronchopneumonia. Death has occurred from within 15 min to 15 h after ingestion.

Rabbits inhaling steam (cooled to body temperature) containing Eucalyptus Globulus Leaf Oil died; the output of respiratory tract fluid was significantly augmented at 19,683 mg/kg; lower doses had no effect on the volume of respiratory tract fluid.

In humans, inhalation of Eucalyptus Globulus Leaf Oil, either as liquid or aerosol, may result in pneumonitis. Inhalation of vapor may be used medicinally and there are no data available on toxicity by this route. Respiratory problems include bronchospasm, tachypnea, pulmonary edema, respiratory depression, and pneumonitis following aspiration of the oil. Eucalyptus Globulus Leaf Oil inadvertently given intranasally has caused irritated nasal mucous membranes.

An aqueous Eucalyptus Globulus Leaf Extract (2000 mg/kg/d) orally administered to mice for 10 days caused no mortalities but necropsy showed pale livers; histological examination of the treated mice showed damage to hepatic cells manifested by swollen hepatocytes with vacuolated cytoplasm.

In short-term oral toxicity studies, Eucalyptus Globulus Leaf Extract administered to rats showed hepatic effects in some studies and none in others. In a 2-week study, activity of SOD was increased in the liver starting at 100 mg/kg with an increase in the level of MDA in the liver of all treatment groups and in the serum at 120 mg/kg. In another study, the NOAEL for males was 1000 mg/kg based on hyaline droplet nephropathy at all dose levels (only observed in male rats); however this response is considered to be rat specific and to have no counterpart in man. In contrast, Eucalyptus Globulus Leaf Extract (130 mg/dry leaves/kg) administered in drinking water for 42 days to rats resulted in no mortalities or toxic effects to the kidneys or livers.

In short-term oral toxicity studies, Eucalyptus Globulus Leaf Oil caused hepatic effects in both mice and rats. Oral

administration of Eucalyptus Globulus Leaf Oil for 84 days caused hepatic effects at 2.0 mL/kg in mice, but no effects were observed in the kidneys. In another study where Eucalyptus Globulus Leaf Oil was administered to rats for 2 weeks, the LOAEL and NOAEL in female rats could be considered as 300 and 100 mg/kg/day, respectively, based on the clinical signs at 300 and 1000 mg/kg/day and increased liver weight at 1000 mg/kg/day. The LOAEL in male rats could be considered as 100 mg/kg bw/day. There were relatively moderate pathological changes in the liver as congestion of the blood vessels in the portal area associated with inflammatory infiltration in rats administered Eucalyptus Globulus Leaf Oil (233 mg/kg) by gavage every 3 days for 30 days. In contrast, rats administered Eucalyptus Globulus Leaf Oil for 30 days showed no clinical signs and the serum biochemical parameters were similar between groups except that there were significant differences between the control group and the mid- and high-dose groups (792 and 1188 mg/kg) for: aspartate transaminase (higher), creatinine (higher), and glucose (lower).

In a combined repeated dose and reproduction/developmental study of Eucalyptus Globulus Leaf Extract administered to rats, the NOAEL for the females was considered to be 300 mg/kg/day for systemic toxicity, based on lower body weight gain and feed consumption during gestation. The NOAEL for developmental toxicity was 300 mg/kg/day, which was based on lower offspring bodyweight gain, and clinical signs that were only observed in the 1000 g/kg/day group. This effect may be associated with test material entering the milk. However, a NOAEL at 300 mg/kg/d was determined for systemic effect in the offspring based on the magnitude of the weight reduction which was quite high. The effects on offspring body weight were not selective and have been observed at a dose producing maternal toxicity and therefore the substance was not considered to be a selective reproductive toxicant. The NOAEL for reproductive toxicity was 1000 mg/kg/day, since no adverse effects were observed.

Eucalyptus Globulus Leaf Extract was not mutagenic, with and without metabolic activation, at up to 5000 µg/plate in an In Vitro Mammalian Cell Gene Mutation Test using mouse lymphoma cells.

Eucalyptus Globulus Leaf Oil at 0.12 and 0.25 µL/mL was found to increase the mitotic instability of the original diploid strain and the number of diploid mitotic recombinants of *A. nidulans*. The genotoxicity of the oil was associated with the induction of mitotic crossing-over or with oil-broken chromosomes. Eucalyptus Globulus Leaf Oil was not genotoxic in a bacterial reverse mutation assay at up to 5000 µg/plate, with and without metabolic activation. Eucalyptus Globulus Leaf Oil was not genotoxic in an in vitro mammalian chromosome aberration test using human lymphocytes (up to 1000 µg/mL) and an in vitro mammalian cell gene mutation test using mouse lymphoma L5178Y cells (up to 300 µg/mL).

In mice treated with a single dose of DMBA, papillomas were observed on 4 of 14 mice dermally administered 0.25 mL Eucalyptus Globulus Leaf Oil (neat) weekly for 33 weeks; none of the 13 control mice had papillomas.

Slight erythema was observed in 5 of 10 rabbits, moderate erythema in 3 of 10 rabbits, and moderate edema in 10 of 10 rabbits dermally administered 5000 mg/kg Eucalyptus Globulus Leaf Oil (neat).

Eucalyptus Globulus Leaf Oil (1 mL) caused moderate conjunctival irritation in all treated eyes 1 h after treatment. Conjunctival irritation was minimal at the 24- and 48-h observations in rabbits and all treated eyes appeared normal at 72 h.

In a retrospective study of dermatologic patients during the years 2010 to 2015, of the 22 subjects that were tested for sensitization to Eucalyptus Globulus Leaf Oil, 1 tested positive. In a retrospective study of dermatologic patients during the years 2000 to 2007, 4 of 679 (0.6%) had positive results for Eucalyptus Globulus Leaf Oil (2%). In patch tests of subjects (n = 96) with dermatitis and/or eczema, 5 subjects had positive reactions to Eucalyptus Globulus Leaf Oil (2% in petrolatum). Two of the subjects were scored with a +/- reaction, 2 with a + reaction, and 1 with a ++ reaction. In a retrospective study of dermatologic patients during the years 2000 to 2009, of the 6680 subjects that were tested for sensitization to Eucalyptus Globulus Leaf Oil, 0.24% had positive reactions. In a cross-sectional study conducted in Belgium (2000 to 2009) of 301 subjects having had reactions to fragrance mixes, a reaction was confirmed to "eucalyptus oil" in 1 of 23 bath and shower products and 1 in 88 skin care products. In sensitization tests of subjects (n = 200) in Poland with dermatitis, 3 subjects had positive reactions to Eucalyptus Globulus Leaf Oil (concentration not specified). When this study was continued on subjects (n = 450) with dermatitis, 5 subjects had a positive reaction to Eucalyptus Globulus Leaf Oil (concentration not specified). In sensitization tests (method not clear) of subjects (n = 5315) in London with dermatitis, 1 subject had a positive reaction to Eucalyptus Globulus Leaf Oil (concentration not specified).

In case reports of exposure to Eucalyptus Globulus Leaf Oil, dermal effects ranged from none to eczema, erythematous macular lesions, papules and vesicles, and/or pruritus. Oral effects included esophageal pain, gasping for breath, restlessness, dyspnea, weak pulse, vomiting, drowsiness, and convulsions. Inhalation effects included strong characteristic smell on the breath, coughing, chest tightness, dyspnea, hoarseness, and wheezing. In children, effects included nasal and epigastric burning, nausea, vomiting, dizziness, muscular weakness, miosis, tachycardia, and a feeling of suffocation. Cyanosis, delirium, and convulsions may be exhibited, especially in infants.

DISCUSSION

To be developed

CONCLUSION

To be developed

TABLES**Table 1.** Definitions and functions of *Eucalyptus globulus*-derived ingredients in this safety assessment.¹

Ingredient	Definition	Function(s)
Eucalyptus Globulus Leaf Oil 8000-48-4	Eucalyptus Globulus Leaf Oil is the volatile oil obtained from the leaves of <i>Eucalyptus globulus</i> and other species of <i>Eucalyptus</i> .	Fragrance ingredient; skin-conditioning agent - miscellaneous
Eucalyptus Globulus Leaf	Eucalyptus Globulus Leaf [<i>is</i>] the leaves of <i>Eucalyptus globulus</i> .	Skin-conditioning agent - miscellaneous
Eucalyptus Globulus Leaf Extract 84625-32-1	Eucalyptus Globulus Leaf Extract is the extract of the leaves of <i>Eucalyptus globulus</i> .	Skin-conditioning agent – miscellaneous, Skin-conditioning agent - occlusive
Eucalyptus Globulus Leaf Powder	Eucalyptus Globulus Leaf Powder is the powder obtained from the dried, ground leaves of <i>Eucalyptus globulus</i> .	Abrasive
Eucalyptus Globulus Leaf/Twig Oil	Eucalyptus Globulus Leaf/Twig Oil is the volatile oil obtained from the leaves and twigs of <i>Eucalyptus globulus</i> .	Fragrance ingredient
Eucalyptus Globulus Leaf Water	Eucalyptus Globulus Leaf Water is an aqueous solution of the steam distillate obtained from the leaves of <i>Eucalyptus globulus</i> .	Fragrance ingredient

Table 2. Chemical and physical properties of *Eucalyptus globulus*-derived ingredients.

Property	Value	Reference
Eucalyptus Globulus Leaf		
Odor	Aromatic, camphoric	11
Eucalyptus Globulus Leaf Oil		
Physical Form	Mobile liquid	67
	Liquid/oil	10
	Liquid	9
Color	Pale yellow	67
	Colorless to pale yellow	10
	Clear, yellow to pale yellow	9
Odor	Fresh, cineol-like	67
	Terpene-like, harsh, conifer/fresh, characteristic of 1,8-cineole, minty, camphoraceous/hay- and cumic-like, rosemary/wood, dusty, powdery	21
Density @ 20°C	0.913 to 0.92	9
@ 20°C	0.909	9
Specific Gravity @ 20°C	0.907	67
	0.9005 to 0.930	21
Melting Point °C	< -20	9
Boiling Point °C	153 to 184	9
Water Solubility	Insoluble	10
Other Solubility		
Alcohol (70%)	Soluble	10
Alcohol (90%)	Miscible	10
Eucalyptus Globulus Leaf/Twig Oil		
Physical Form	Liquid	11
Color	Colorless or pale yellow	11
Odor	Aromatic, camporic	11
Specific Gravity	0.9005 to 0.930	21
Other Solubility		
Ethanol	Soluble	11

Table 3. Methods of manufacture reported in the literature.

Ingredient	Method	Reference
Eucalyptus Globulus Leaf Oil	Freshly collected <i>Eucalyptus</i> leaves were cleaned by using distilled water and air-dried at room temperature under shade. The leaves were then chopped in to small pieces and essential oil extraction by hydro-distillation in a modified Clevenger-type apparatus. The oil was filtered and concentrated using rotary evaporator.	³⁹
Eucalyptus Globulus Leaf Oil	<i>Eucalyptus globulus</i> leaves were air-dried. Dried leaves (25 g) were mixed with 500 mL of water and subjected to hydro-distillation for 3 h. The resulting volatile oils were dried over anhydrous sodium sulfate and then stored in dark bottles in a refrigerator until used.	⁴¹
Eucalyptus Globulus Leaf Oil	Eucalyptus Globulus Leaf Oil used for medicinal purposes is manufactured from fresh leaves or fresh terminal branchlets of <i>Eucalyptus globulus</i> plants. Oil is extracted by steam distillation and rectification.	¹²
Eucalyptus Globulus Leaf Extract	Freshly collected <i>Eucalyptus globulus</i> leaves were air-dried followed by milling into a powder. The powder (5 g) was mixed in 200 mL of distilled water overnight, and then filtered through cheese cloth.	⁴³
Eucalyptus Globulus Leaf Extract	Freshly collected <i>Eucalyptus globulus</i> leaves were air-dried followed by milling into a powder. The powder (200 g) was then percolated in distilled water (500 mL) for 2 weeks. The percolated mixture was filtered and evaporated on a water bath.	⁴⁴
Eucalyptus Globulus Leaf Extract	The extract was prepared by powdering <i>Eucalyptus globulus</i> leaves. The leaves were then macerated in 80% aqueous ethanol for one week with occasional shaking. The resulting extract was filtered and concentrated to a dark green residue under reduced pressure on a rotary evaporator. The yield was approximately 6%.	⁴⁵

Table 4. Constituents of *Eucalyptus globulus*-derived ingredient reported to the ECHA database from various suppliers (concentrations were not provided).⁹

Constituent	Eucalyptus Globulus, Extract	Eucalyptus Globulus Oil, Rectified	Rectified Eucalyptus Oil	Eucalyptus Globulus Oil, Rectified	Eucalyptus Globulus Oil, Steam Distilled	Eucalyptus Globulus Oil, Rectified
Bornan-2-one	-	-	-	-	-	+
Camphene	-	-	-	-	+	-
1,8-Cineole	+	+	+	+	+	+
p-Cymene	+	+	+	+	+	-
[1aR-(1a α ,4a α ,7a β ,7b α)]-Decahydro-1,1,7-trimethyl-4-methylene-1H-cycloprop[e]azulene	-	-	-	-	+	-
(Z)-3,7-Dimethylocta-1,3,6,-triene	-	-	-	-	+	-
Dipentene	+	+	+	+	+	-
Isovaleric acid	-	-	-	-	+	-
p-Menth-1-en-8-ol	-	+	+	+	+	-
p-Menta-1,4-diene	+	+	+	+	+	-
p-Menta-1,5-diene	-	+	+	+	+	+
(R)-p-Menta-1,8-diene	-	-	-	-	-	+
7-Methyl-3-methyleneocta-1,6-diene	-	+	-	+	+	-
Pin-2(3)-ene	+	+	+	+	+	+
Pin-2(10)-ene	-	+	+	+	+	+
(\pm)-2(10)-Pinen-3-one	-	-	-	-	+	-
Thuj-4(10)-ene	-	-	-	-	-	+
Unknown constituents	-	+	-	+	+	+

Table 5. Constituent groups found in *Eucalyptus globulus* leaf extracts using different extract mediums.⁷

Phytochemicals	Petroleum			
	Ether Extract	Chloroform Extract	Methanol Extract	Aqueous Extract
Alkaloids	-	-	-	-
Carbohydrate	+	+	+	+
Proteins and amino acids	-	-	-	-
Phytosterols	-	+	+	-
Phenolic compounds and tannins	-	-	+	+
Saponins	-	-	+	+
Triterpenoids	-	+	+	-
Flavonoids	-	-	+	-

Table 6. The ranges constituents of Eucalyptus Globulus Leaf Oil (essential oil).⁶

Constituent	Content (%)
1,8-Cineole	65.4 – 83.9
α -Pinene	3.7 – 14.7
(+)-Limonene	1.8 – 9.0
Globulol	Trace – 5.3
(E)-Pinocarveol	2.3 – 4.4
p-Cymene	1.2 - 3.5
(+)-Aromadendrene	1.2 – 3.5
Pinocarvone	Trace – 1.0

Table 7. Comparison of chemical composition of the essential oil from *Eucalyptus globulus* leaves collected from different locations extracted by steam distillation.^{20,22,23}

Compounds	Algeria (%)	China (%)	Northern Ethiopia (%)
α -Pinene	24.600	9.22	*
Camphene	0.117	*	0.164-0.269
β -Pinene	0.217	*	0.957-1.237
1,8-Cineol	51.083	72.71	66.283-75.361
α -Campholenal	0.390	*	*
Fenchol	0.179	*	*
L-pinocarveol	9.987	*	*
Borneol	0.346	*	*
4-Terpineol	0.178	*	*
Caren-4-ol	0.195	*	*
α -Terpineol	0.486	2.54	1.505-2.256
Myrtenol	0.202	*	*
cis-Carveol	0.187	*	*
Globulol	2.817	2.77	0.819-1.431
α -Terpineol acetate	1.2	3.11	2.188-3.391
Alloaromadendrene	*	2.47	*
Cis-Ocimen	*	*	15.923-21.331
β -Myrcene	*	*	0.658-1.004
Aromadendrene	*	*	0.694-2.858
Total identified	92.184	92.82	89.191-109.138

* Not found or found at <1%.

Table 8. The constituents of Eucalyptus Globulus Leaf Oil reported by a supplier.⁶⁷

Constituent	Content (%)
α -Pinene	1.2
β -Pinene	0.6
α -Phellandrene	1.0
Limonene	7.7
β -Phellandrene	0.3
<i>p</i> -Cymene	3.2
1,8-Cineole	78.8
γ -Terpinen	4.4
Terpinen-4-ol	0.2
α -Terpineol	0.3
Camphor	0.0

Table 9. Constituents of concern found in *Eucalyptus globulus* leaves and oil.

Constituent	Concern	References
Geraniol	Potential dermal sensitizer	²⁻⁶
Limonene	Hydroperoxides are potential dermal sensitizers	^{2,6,68}
Linalool	Hydroperoxides are potential dermal sensitizers. Safe at up to 4.3% (20% in a consumer fragrance)	^{2,69}
β -Myrcene	Oral dosing for 2 years caused kidney cancers in male rats (0.25 g/kg) and liver cancer in male mice (0.25 g/kg); may be related to the occurrence of kidney tumors in female rats and liver tumors in female rats. Associated with other lesions of the kidney in rats, the liver in mice, and the nose in male rats.	⁷⁰
Phellandrene	Potential carcinogen promoter. Secondary treatment at 40% after treatment with 9,10-dimethyl-1,2-benzanthracene (DMBA) increased number of papillomas in mice.	^{46,71}
α -Pinene	Potential carcinogen. Increased incidence of transitional epithelium hyperplasia of urinary bladder in male and female mice at 100 ppm or more, the severity of which increased with increasing exposure concentration.	^{71,72}
Quercetin	Positive genotoxic effect in an Ames assay Consistently genotoxic in <i>in vitro</i> tests and in some <i>in vivo</i> studies of i.p. exposures, but was consistently nongenotoxic in oral exposure studies	^{24,25}

Table 10. Constituents of *Eucalyptus globulus* leaves and oil that have IFRA standards.⁷³

Constituent	Standard Limits
2-Phenylacetaldehyde	Limited to 0.01% - 2.9%, depending on use category due to sensitization.*
Benzyl benzoate	Limited to 2% - 42.8%, depending on use category due to sensitization.*
Butyraldehyde	Limited to 0.17% - 5%, depending on use category due to sensitization *
Carvone	Limited to 0.08% - 5%, depending on use category due to sensitization.*
Citronellol	Limited to 0.8% - 21.4%, depending on use category due to sensitization.*
Cuminaldehyde	Limited to 0.03% - 5%, depending on use category due to sensitization.*
<i>trans</i> -β-Damascenone	Limited to 0.2% in fragrances and Eau de Toilette; 0.01% in other leave-on and rinse-off products; and 0.2% in non-skin, and incidental skin contact products due to carcinogenicity.
Estragol	Limited to 0.2% - 4.3%, depending on use category due to sensitization.*
Eugenol	Limited to 0.2% - 4.3%, depending on use category due to sensitization.*
Geraniol	Limited to 0.03% - 8.6%, depending on use category due to sensitization.*
Ionone (mixed isomers)	Limited to 2% - 50.72%, depending on use category due to sensitization*
Limonene	<i>d</i> -, <i>l</i> -and <i>dl</i> -Limonene and natural products containing substantial amounts of it, should only be used when the level of peroxides is kept to the lowest practical level, for instance by adding antioxidants at the time of production. Such products should have a peroxide value of less than 20 mM peroxides per liter.
Linalool	Limit peroxide level to 20 mmol/L due to sensitization. Linalool and natural products known to be rich in linalool, such as bois de rose, coriander or ho wood oil, should only be used when the level of peroxides is kept to the lowest practical level. It is recommended to add antioxidants at the time of production of the raw material. The addition of 0.1% BHT or alpha-tocopherol for example has shown great efficiency. The maximum peroxide level for products in use should be 20 mmol/L.
Phenylacetaldehyde	Limited to 0.02% - 3%, depending on use category due to sensitization.*
Safrole	Not to be used as a fragrance ingredient. Essential oils containing safrole are not to exceed 0.01% in consumer products.

IFRA - International Fragrance Association

* Use categories are based on types of skin contact (e.g., skin, lips), length of contact (e.g., leave-on, rinse-off), or type of use (e.g., mouthwash)

Table 11. Frequency of use according to duration and exposure of *Eucalyptus globulus*-derived ingredients.²⁶

Use type	Maximum Concentration (%) Uses	Maximum Concentration (%) Uses	Maximum Concentration (%) Uses	Maximum Concentration (%) Uses
	Eucalyptus Globulus Leaf Oil	Eucalyptus Globulus Leaf	Eucalyptus Globulus Leaf Extract	Eucalyptus Globulus Leaf Powder
Total/range	414	5.5	NR	1.2
<i>Duration of use</i>				
Leave-on	208	5.5	NR	NR
Rinse-off	151	0.74	NR	1.2
Diluted for (bath) use	55	0.2	NR	NR
<i>Exposure type</i>				
Eye area	2	0.00001-0.038	NR	NR
Incidental ingestion	4	0.008-0.74	NR	NR
Incidental Inhalation-sprays	17; 81 ^a ; 33 ^b	0.00056-0.4; 0.00001-0.74 ^a	NR	NR
Incidental inhalation-powders	4 ^c ; 33 ^b	0.001-5.5 ^c	NR	NR
Dermal contact	356	0.000002-5.5	NR	1.2
Deodorant (underarm)	3 ^a	NR	NR	NR
Hair-noncoloring	51	0.00001-0.12	NR	NR
Hair-coloring	1	0.005	NR	NR
Nail	2	0.0001-0.15	NR	NR
Mucous Membrane	116	0.00013-0.74	NR	NR
Baby	7	0.000002-0.00067	NR	NR
	Eucalyptus Globulus Leaf Water		“Eucalyptus”^d	
Total/range	NR	0.02-1.4	41	NS
<i>Duration of use</i>				
Leave-on	NR	1.4	32	NS
Rinse-off	NR	0.02-0.1	2	NS
Diluted for (bath) use	NR	NR	7	NS
<i>Exposure type</i>				
Eye area	NR	NR	NR	NS
Incidental ingestion	NR	NR	NR	NS
Incidental Inhalation-sprays	NR	NR	10; 2 ^a ; 8 ^b	NS
Incidental inhalation-powders	NR	1.4 ^c	8 ^b	NS
Dermal contact	NR	0.02-1.4	38	NS
Deodorant (underarm)	NR	NR	NR	NS
Hair-noncoloring	NR	0.02-0.1	1	NS
Hair-coloring	NR	NR	NR	NS
Nail	NR	NR	2	NS
Mucous Membrane	NR	NR	9	NS
Baby	NR	NR	NR	NS

NR = Not Reported; NS = Not Surveyed; Totals = Rinse-off + Leave-on + Diluted for Bath Product Uses.

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

^a It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

^b Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

^c It is possible these products may be powders, but it is not specified whether the reported uses are powders.

^d “Eucalyptus” is not an INCI name but was reported in the VCRP. It is not known if this is a cosmetic ingredient in this report.

Table 12. Dermal penetration enhancement studies of Eucalyptus Globulus Leaf Oil.

Ingredient/substance	Drug	Details	Results	Reference
Eucalyptus Globulus Leaf Oil (82.9% cineole) tested at 5%, 10%, 20%, or 50% v/v in distilled water	CHG 2% w/v	Thawed, full-thickness human breast skin from 3 donors. Skin was placed in vertical Franz diffusion cells (3.14 cm^2). Receptor cells filled with PBS. CHG (2% w/v) was also mixed with Eucalyptus Globulus Leaf Oil (10% v/v) and isopropyl alcohol (70% v/v) and distilled water. Mixtures without CHG were used as controls. Polysorbate 80 (0.1% v/v) was added to enhance solubility of oil. Test mixtures (1 mL) were spread on skin surface. Skin was removed and examined at 2 and 30 min, and 24 h. Punches of skin samples were sectioned horizontally and HPLC was used to measure the CHG in skin samples. In an additional 24-h permeation study: CHG, with and without 50% Eucalyptus Globulus Leaf Oil. Receptor fluid was sampled every 30 min for 2 h, every 60 min between 2 to 6 h, and at 8 h, 12 h and 24 h.	Generally, dermal penetration of CHG increased in a concentration-dependent manner of the Eucalyptus Globulus Leaf Oil through skin samples over 24 h. Eucalyptus Globulus Leaf Oil at 5% facilitated greater CHG skin penetration to the deeper layers of the skin (below 300 μm) and 10% (v/v) Eucalyptus Globulus Leaf Oil enhanced CHG skin penetration in upper 900 μm . There were no significant differences in CHG concentration measured in skin with 10% and 20% Eucalyptus Globulus Leaf Oil. Eucalyptus Globulus Leaf Oil at 50% enhanced penetration of CHG into lower layers of skin within 2 min; CHG concentrations achieved at depths of 300 to 1500 μm were between 0.019 and 0.043 $\mu\text{g}/\text{mg}$ tissue. At 30 min, concentration of CHG in upper 100 μm was 0.398 (± 0.076) $\mu\text{g}/\text{mg}$ tissue. Combining 10% Eucalyptus Globulus Leaf Oil and CHG in 70% isopropyl alcohol significantly enhanced CHG dermal penetration compared to CHG and isopropyl alcohol 0.121 ± 0.019 vs $0.023 \pm 0.007 \mu\text{g}/\text{mg}$ in upper 100 μm of skin. CHG, with and without 50% Eucalyptus Globulus Leaf Oil, was detected at negligible levels in receptor compartment over 24 h, suggesting that CHG did not permeate through full skin thickness, and was retained within tissue.	³⁵
Eucalyptus Globulus Leaf Oil (plant parts not specified) 0, 2.5%, 5%, or 7.5%	TMP	Gels to be used in test patches were made containing TMP (15.6%), Carbopol 92P (2.5%), ethanol (5%), Eucalyptus Globulus Leaf Oil (0, 2.5%, 5%, or 7.5%), Polysorbate 80 (2.0%), glycerin (10%), and water. Tests were conducted using modified Keshary-Chien diffusion cells (3.14 cm^2) with either fresh dorsal rat skin or thawed human cadaver skin from chest area. Samples were collected at 1, 3, 5, 7, 9, 12 and 24 h.	Enhancement ratios for Eucalyptus Globulus Leaf Oil (2.5%, 5%, or 7.5%) were 3.38, 4.47, and 4.64, respectively, for rat and human skin. TMP flux across the human chest skin with 5% Globulus Leaf Oil was 17-fold greater (346.0 $\text{mg}/\text{cm}^2/\text{h}$) than the flux (20.1 $\text{mg}/\text{cm}^2/\text{h}$) of a saturated solution of TMP without the oil.	³⁶
Eucalyptus Globulus Leaf Oil (plant parts not specified; 80% to 85% cineol) 5%, 7.5%, and 10%	Ketorolac	A reservoir type transdermal patch was fabricated with a core gel system of a non-ionic polymer, PBS, and isopropyl alcohol.	ERs were 1.80, 3.04, and 3.68 for 5%, 7.5%, and 10%, respectively. When compared with other potential dermal penetration enhancers, the order of effectiveness was: Globulus Leaf Oil > transcutol > DMSO > <i>d</i> -limonene. When a gel incorporated with crushed apricot seed was rubbed onto the skin prior to administration of patch, the ER for the addition of Globulus Leaf Oil (10%) was 5.16.	³⁷
Eucalyptus Globulus Leaf Oil (plant parts not specified) and fractions obtained using a rotary evaporator at 100°C, 110°C, 120°C, 130°C, and 140°C under vacuum.	5-FU	Saturation solution of 5-FU (1 mL saturated solution plus a crystal of 5-FU was placed in donor cell) with and without 150 μL Globulus Leaf Oil for 12 h using clipped abdominal skin of white male rats in a 2-cell diffusion cells (2.01 cm^2)	ERs: Globulus Leaf Oil, 59.63; 100°C fraction, 58.49; 110°C fraction, 59.53; 120°C fraction, 59.16; 130°C fraction, 82.48; and 140°C fraction, 82.55. When compared with other potential dermal penetration enhancers, the order of effectiveness was: azone > Globulus Leaf Oil > peppermint oil > turpentine oil	³⁸

5-FU = 5-Fluorouracil; CHG = chlorhexidine; DMSO = dimethyl sulfoxide; ER = enhancement ratio; HPLC = high-performance liquid chromatography; PBS = phosphate buffered saline; TMP = 2,3,5,6-tetramethylpyrazine

Table 13. Genotoxicity studies of *Eucalyptus globulus*-derived ingredients and substances.

Ingredient/substance	Assay	Details	Results	References
Eucalyptus Globulus Leaf Extract	In vitro mammalian cell gene mutation test	OECD GL 476 using mouse lymphoma L5178Y cells. Without S9 mix (3-h exposure): 10, 100, 150, 200, 225, 250, 275 and 300 µg/mL; Without S9 mix (3-h exposure, additional test): 10, 100, 115, 130, 145, 160, 175, 190, 210, 225, 250 and 300 µg/mL in acetone; With S9 mix (3-h exposure): 10, 100, 115, 130, 145, 160, 175, 190, 210, 225, 250 and 300 µg/mL in acetone; Without S9 mix (24-h exposure): 10, 50, 100, 150, 175, 200, 225, 250, 275 and 300 µg/mL in acetone.	Not mutagenic with or without metabolic activation	⁹
Eucalyptus Globulus Leaf Oil	Bacterial reverse mutation assay	OECD GL 471; <i>S. typhimurium</i> (strains: TA98, TA100, TA1535, and TA1537) and <i>E. coli</i> (WP2) Experiment 1 (plate incorporation method): 0, 5, 15, 50, 150, 500, 1500 and 5000 µg/plate in DMSO with and without metabolic activation Experiment 2 (pre-incubation method): 0, 50, 150, 500, 1500 and 5000 µg/plate in DMSO with and without metabolic activation Positive control substances: 4-nitroquinoline-N-oxide, 2-nitrofluorene, sodium azide without metabolic activation Positive control substance: benzo(a)pyrene; 2-Aminoanthracene with metabolic activation.	Negative for genotoxicity with and without metabolic activation. Positive for cytotoxicity in Experiment 2 at 5000 µg/plate in the absence of S9 mix.	⁹
Eucalyptus Globulus Leaf Oil	In vitro mammalian chromosome aberration test	OECD GL 473 using human lymphocytes with and without metabolic activation. - Without S9 mix (3 h treatment and 18 h recovery): 10, 20, 40, 60, 80 and 1000 µg/mL in acetone - With S9 mix (3 h treatment and 18 h recovery): 100, 150, 200, 250, 275, 300, 325 and 350 µg/mL in acetone - Without S9 mix (21 h continuous treatment): 50, 60, 70, 80, 90, 100, 110 and 120 µg/mL in acetone. Positive control: mitomycin C 0.2 µg/mL (3-h treatment) and 0.1 µg/mL (21-h continuous treatment) without metabolic activation. Cyclophosphamide 5 µg/mL (3-h treatment) with metabolic activation.	No statistically significant increases in the chromosomal aberrations, polyploid or endoreduplicated metaphase cells were observed under any treatment condition at any concentration, with or without metabolic activation, when compared to the vehicle control. Cytotoxicity was observed in various concentrations and doses were selected based on the mitotic index data. The controls had the expected result.	⁹
Eucalyptus Globulus Leaf Oil	In vitro mammalian cell gene mutation test	OECD GL 476 using mouse lymphoma L5178Y cells. Without S9 mix (3-h exposure): 10, 100, 150, 200, 225, 250, 275 and 300 µg/mL in acetone; Without S9 mix (3-h exposure, additional test): 10, 100, 115, 130, 145, 160, 175, 190, 210, 225, 250 and 300 µg/mL in acetone; With S9 mix (3-h exposure): 10, 100, 115, 130, 145, 160, 175, 190, 210, 225, 250 and 300 µg/mL in acetone; Without S9 mix (24-h exposure): 10, 50, 100, 150, 175, 200, 225, 250, 275 and 300 µg/mL in acetone. Positive control substance: methylmethanesulfonate: 10 µg/mL (3-h exposure); 5 µg/mL (24-h exposure) without metabolic activation; benzo(a)pyrene: 1 µg/mL (3-h exposure) with metabolic activation.	Not mutagenic with or without metabolic activation	⁹
Eucalyptus Globulus Leaf Oil	Somatic segregation assay using diploid strain of fungus <i>Aspergillus nidulans</i> , heterozygous for nutritional and conidia color markers. 0.12 and 0.25 µL/mL	Using diploid strain of fungus <i>A. nidulans</i> , heterozygous for nutritional and conidia color markers. 0.12 and 0.25 µL/mL Test substance: eucalyptol (49.0 %), α-pinene (8.9%), β-pinene (1.5%), globulol (6.9%), α-eudesmol (1.12%), spathulenol (1.42%), γ-cadinene (1.45%), trans-β-elemenone (1.23%) and aromandendrene (2.3%), totaling 74 % of oil.	Increased mitotic instability of original diploid strain and number of diploid mitotic recombinants of <i>A. nidulans</i> . Genotoxicity of the oil was associated with induction of mitotic crossing-over or with oil-broken chromosomes.	¹²

DMSO = Dimethyl sulfoxide; OECD GL = Organisation for Economic Co-operation and Development Guideline

Table 14. Retrospective and multicenter studies of Eucalyptus Globulus Leaf Oil.

Concentration	n	Details	Results	Reference
Not specified	22	Retrospective study of dermatologic patients during the years 2010 to 2015 was conducted at the Contact Allergy Unit of the University Hospitals of Leuven	1 tested positive	²
2%	679	In patch tests conducted in 2000 to 2007 of cosmetic ingredients in subjects with suspected contact dermatitis from cosmetic products by the Mayo Clinic Contact Dermatitis Group	4 (0.6%) had positive results; 2 of these subjects had reactions with macular erythema and 2 had weak reactions	⁴⁸
2% in petrolatum	96	Patch tests of subjects in a practice that specializes in contact dermatitis and eczema	5 subjects had positive reactions; 2 of the scored with a +/- reaction, 2 with a + reaction, and 1 with a ++ reaction	⁴⁹
2% in petrolatum	6680	Patch tests of subjects with dermatitis and/or eczema (2000 to 2008) by the Information Network of Departments of Dermatology (IVDK)	0.24% of those tested had positive reactions; 0.41% scored with a ?/ irritant reaction, 0.19% with a + reaction, and 0.06 with a ++++ reaction	⁵⁰
Not specified	301 subjects who reacted to a fragrance mix	Study (2000 to 2009) of “presence confirmed” of fragrance allergens in cosmetic products to which patients reacted positively in the Department of Dermatology, Contact Allergy Unit, University Hospital St Rafael, Belgium	Reactions were only observed in 1 of 23 bath and shower products and 1 of 88 skin care products, and not the other 13 cosmetic product categories, containing “eucalyptus oil”	⁵¹
Not specified	200	Patch tests of subjects with dermatitis at the Warsaw Medical School, Poland	3 subjects had positive reactions	⁵²
Not specified	450	Patch tests of subjects with dermatitis at the Warsaw Medical School, Poland	5 subjects had positive reactions	⁵³
Not specified	5315	Patch tests of subjects with dermatitis at the Warsaw Medical School, Poland	1 subject had a positive reaction	⁵⁴

Table 15. Case reports of Eucalyptus Globulus Leaf Oil.

Summary	Dermal	Reference
An 8-year-old-girl presented with a 3-day history of erythematous lesions on her neck, which appeared one day after the use of an inhalant ointment. The ointment consisted of Eucalyptus Globulus Leaf Oil and spruce oil (ratio not provided) and had been applied nightly to the collar of the girl’s clothing for an unspecified period of time. She presented with dusky red color, nummular patch that was 6 cm in diameter on her neck and a similar patch that was 4 cm diameter on her right upper clavicular area. She had a sharply-bordered erythematous macular lesion on her neck and upper chest. Patch testing was performed with the European baseline series using Finn Chambers (8 mm) for 48 h. The concentration and vehicle of the Eucalyptus Globulus Leaf Oil was not specified; the spruce oil was tested at 5% in petrolatum. Readings were taken at 30 min and 4 days after removal. Eucalyptus Globulus Leaf Oil had a positive reaction (++) as did the spruce oil (+++). The test was conducted on healthy controls ($n = 3$) with negative results.		⁵⁶
Eucalyptus Globulus Leaf Oil was used to treat a male subject who had chronic postoperative osteomyelitis of the right femur with a draining sinus that failed to respond to ciprofloxacin and rifampicin during 2 years of antibiotic therapy. The infected site was treated with a cream containing Eucalyptus Globulus Leaf Oil (1.0 g/day) to the sinus for 5 days and no antibiotics were used. The wound was completely healed at 2 weeks and no adverse effects from the Eucalyptus Globulus Leaf Oil were reported.		⁵⁸
Eucalyptus Globulus Leaf Oil was used to treat a 42-year-old man an infection after a mid-foot fracture and dislocation. The infected tissue was surgically debrided and a cream containing Eucalyptus Globulus Leaf Oil (0.5 g/day) was applied for 3 weeks. No antibiotics were used. The subject was clear of infection at 12 weeks with no adverse effects from Eucalyptus Globulus Leaf Oil were reported.		⁵⁸
A 12-year-old boy splashed Eucalyptus Globulus Leaf Oil (amount unknown) on his face. No symptoms developed.		⁵⁹
A 4-year-old boy was placed in a bath containing Eucalyptus Globulus Leaf Oil (amount unknown). He developed redness, irritation, and burning sensation on his buttocks and penis soon after being placed in the water. He was removed from the bath and rinse with water. The irritation resolved within 1 h.		⁵⁹

Table 15. Case reports of Eucalyptus Globulus Leaf Oil.

Summary	Reference
A 6-year-old girl presented with slurred speech, ataxia and muscle weakness progressing to unconsciousness following the widespread application of a home remedy for urticaria. This remedy consisted of: apple cider vinegar (200 mL), olive oil (200 mL), methylated spirits (200 mL); 95% ethanol (containing no methanol), and Eucalyptus Globulus Leaf Oil (50 mL; double distilled, containing 80% to 85% cineole oil). The concoction (approximately 400 mL) had been applied to her limbs and trunk under plastic wrap and the dressing changed every 2 to 4 h for 2 days. When she was not improving, the amount of Eucalyptus Globulus Leaf Oil was doubled in the concoction. Within 10 to 15 min of applying the bandages, she appeared "intoxicated" with slurred speech and unsteady gait. She improved following removal of the topical preparation and bathing but was still drowsy, nauseated, and vomiting. After a night in the hospital, her symptoms resolved, with no long-term effects.	55
A 65-year-old, otherwise healthy woman, who worked as an aromatherapist presented with eczema on her arms and upper trunk, which later spread to her legs, face, and hands. She had no history of skin disease in herself or her family. Her hand eczema became chronic and associate with handling household cleansers, sealing wax, paints, and the essential oils, which she diluted herself. When patch tested with Finn Chambers, she had a ++ reaction to Eucalyptus Globulus Leaf Oil at 5% in petrolatum, but not at 1%.	57
A 27-year-old professional athlete had been using an analgesic and anti-inflammatory cream for 2 years before pruritus and erythema appeared on the toes of the left foot. The next application of the cream caused papules and vesicles, with increasing pruritus. A topical corticosteroid relieved his symptoms; he still had a vesicular scaly eczema on the dorsa of the toes of the left foot. Patch testing with TRUE Test™ standard allergens and the Chemotechnique cosmetics series was negative. Eucalyptus Globulus Leaf Oil (1% in petrolatum) gave a ++ reaction to at Days 2 and 4; the other ingredients of the cream were negative. The controls were all negative at Days 2 and 4.	60
Oral	
After an evening meal an adult male took a large teaspoonful of Eucalyptus Globulus Leaf Oil. He immediately experienced esophageal pain followed by gasping for breath, restlessness, and convulsive movements of his hands. He was semi-comatose passing to coma. Vomiting was induced prior to him becoming comatose and he gradually recovered consciousness being quite well by next morning.	10
An adult male who took 10 mL to 15 mL of Eucalyptus Globulus Leaf Oil became ataxic and faint within 10 min. He soon had distressing dyspnea, weak pulse, and violent vomiting. His skin was greenish-yellow. Half an hour after ingestion he was very drowsy, had painful and excessive micturition and was experiencing violent diarrhea. For 3 days he was drowsy, ataxic and his skin retained the chlorotic hue. For nearly 2 weeks his breathe, feces, and skin smelt of the oil and it was a full 2 weeks before he fully recovered.	10
An adult male took approximately 25 mL of Eucalyptus Globulus Leaf Oil. Within 2 h he was dazed and friends successfully induced vomiting. Four hours after ingestion he was cyanosed with labored breathing, foam in the mouth, congestion, rhonchi, and moist rales throughout both lungs. He was administered oxygen with a stimulant and 5 to 6 h later was recovered enough to answer questions. However 13 h after ingestion he complained of difficulty and pain in drawing his breathe. Breathing became more rapid and labored and his pulse was quick and thready. He died 40 h after taking the oil. Death was presumed to be due to bronchopneumonia.	10
An adult who ingested 120 to 220 mL Eucalyptus Globulus Leaf Oil had severe poisoning and was successfully treated with mannitol, hemodialysis, and peritoneal dialysis.	10
A 7 month old boy was offered a teaspoonful of <i>Eucalypt</i> Eucalyptus Globulus Leaf Oil. He coughed, choked and some of the oil was spilled. His skin was pale. He collapsed with rapid shallow respirations and feeble pulse 25 min after ingestion later. Limbs were flaccid, pupils pin-point, rhonchi was heard at both bases. His stomach was washed out (gavage?) and 3 h later he was showing spontaneous movement. At 24 h his general state was good. The odor stayed on his breath for 72 h.	61
A 6-year-old boy took 4 to 5 mL of Eucalyptus Globulus Leaf Oil and exhibited severe vomiting within 2 h. He was semi-comatose 5 h later. There was no coughing and his breathing was shallow. After approximately 8 h, he recovered from the heavy comatose condition and he slept until the next day where he appeared to have recovered. His breathe smelt of Eucalyptus Globulus Leaf Oil for 3 days. In summary the poisoning manifested itself as gastrointestinal irritation and cerebral paresis.	62
A 10-year-old boy ingested approximately 15 mL of Eucalyptus Globulus Leaf Oil. In a few minutes he was gasping for air and vomited heavily once. He was breathing well for about an hour. He then began struggling for air, which increased until his death 15 h after ingestion of the oil. He spoke rationally several times up to less than an hour of his death.	10
A 3-year-old boy ingested 10 mL of Eucalyptus Globulus Leaf Oil. Within 30 min he was deeply comatose and his breath smelt strongly of Eucalyptus Globulus Leaf Oil. Pupils were constricted, muscle tone markedly reduced, and tendon reflexes could not be elicited. Respirations were shallow and irregular. Blood pressure was 75/40 mmHg. Respiratory rate, blood pressure, and pulse returned to normal after 2.5 h. After 5 h, consciousness was gradually regained and by 24 h, physical examination was normal apart from a faint smell of eucalyptus on the breathe.	64
A 6-year-old child was administered approximately 15 mL of Eucalyptus Globulus Leaf Oil and experienced only slight drowsiness.	10
A 2.5-year-old child was found after ingesting Eucalyptus Globulus Leaf Oil (estimated 5 mL). She had no symptoms at first, but after 45 min she was listless and unresponsive. She was taken to the emergency room and administered activated charcoal and a cathartic via a nasogastric tube. She vomited the charcoal. Heartrate after 3 h in the hospital was 117 beats/min. Her CNS symptoms gradually improved and resolved over the next 7 h. She had several apneic episodes during this time.	59
A 29-year-old male accidentally ingested Eucalyptus Globulus Leaf Oil (originally thought to be 3 to 4 ounces, but determined to be approximately 1 ounce (approximately 30 mL)). He immediately started gagging and vigorous vomiting. At the emergency room, he was lavaged and administered activated charcoal and cathartic. Within 40 min, he was drowsy, but not comatose. Pulse ranged from 68 to 80 beats per min and BP ranged from 90/60 to 110/70 mmHg. After approximately 3.5 h, he experienced PVCs-trigeminal runs, described as 1 to every 6 beats to 1 to every 3 beats. The subject has no history of cardiac abnormalities. The cardiac symptoms continued for 8 to 10 h while his BP was around 90/60. Symptoms resolved within 24 h.	59
A 6-year-old boy presented with status epilepticus within 10 min of accidental ingestion of Eucalyptus Globulus Leaf Oil (10 mL). He had eight episodes of tonic-clonic convulsions which were controlled with intravenous phenytoin and valproate. There was no previous history of seizures. His kidney function tests, liver function tests, blood sugar, and serum calcium were normal. His EEG showed spikes. Child improved substantially within 20 h and was discharged.	63
A 3-year-old boy presented with status epilepticus within 10 min of accidental ingestion of Eucalyptus oil (5 mL). He had four episodes of tonic-clonic convulsions which were controlled with i.v. phenytoin. There was no previous history of seizures. His kidney function tests, blood sugar, and serum calcium were normal. He improved and was discharged.	63

Table 15. Case reports of Eucalyptus Globulus Leaf Oil.

Summary	Reference
Inhalation	
Three subjects (age and sex not provided) inhaled Eucalyptus Globulus Leaf Oil (amounts not provided). Symptoms were primarily the strong smell of the oil on the breath and, in 1 case, coughing (this subject did have a cold).	59
A 46-year-old woman with a past medical history of hypothyroidism, migraine headaches, peptic ulcer disease, depression, and allergic rhinitis became ill when she developed a sore throat and complained of episodic dyspnea that appeared primarily at work. She reported that chest tightness and wheezing seemed to be associated with exposure to a <i>Eucalyptus</i> sp. plant. In one instance her respiratory symptoms was severe enough to require hospitalization. Spiral chest computed tomography excluded pulmonary emboli, and high-resolution chest computed tomography showed a few areas of ground-glass densities. She had a normal IgE level (63 IU/mL). She was treated with corticosteroids and bronchodilators but had no improvement in her symptoms. Re-exposure to <i>Eucalyptus</i> sp. plant caused recurrent bouts of chest tightness, dyspnea, cough, hoarseness, and wheezing. She had negative skin test results for immediate hypersensitivity to a variety of inhalant allergens. The patient underwent 2 challenges to <i>Eucalyptus</i> sp. performed 1 month apart. All stimuli were applied to gauze held approximately 5" from the nares. Dry <i>Eucalyptus</i> sp. leaves were used to impregnate the test gauze. The initial challenge was with <i>Eucalyptus</i> and was not masked. There was obvious adduction of the vocal cords within 30 seconds of the inhalation. The second test was water first, followed by ammonia, pine oil, and an ammonia- <i>Eucalyptus</i> mixture. She began to experience the paradoxical vocal cord motion after a few minutes of exposure. The VCD persisted for several minutes after the testing and was exacerbated with talking.	65
The accidental administration of Eucalyptus Globulus Leaf Oil to 9 children (ranging from 1 month to 3 years of age) in the form of nose drops. The children were reported cry out after instillation. All children smelled of eucalyptol. Four had irritated nasal mucous membranes and one had tachycardia. All of their noses were rinsed with NaCl (0.9%). Some of the children were treated with gastric lavage. The symptoms of Eucalyptus Globulus Leaf Oil poisoning were nasal and epigastric burning, nausea, vomiting, dizziness, muscular weakness, miosis, tachycardia, and a feeling of suffocation. Cyanosis, delirium, and convulsions may be exhibited, especially in infants.	66

BP – blood pressure; CNS – central nervous system; EEG = electroencephalogram; PVC - premature ventricular contractions; VCD - vocal cord dysfunction

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**2017 VCRP Data for
Eucalyptus globulus (Eucalyptus)-Derived Ingredients**

02A - Bath Oils, Tablets, and Salts	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	2
02D - Other Bath Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
03D - Eye Lotion	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	2
04C - Powders (dusting and talcum, excluding aftershave talc)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
05A - Hair Conditioner	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	2
05F - Shampoos (non-coloring)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	6
05I - Other Hair Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	7
07C - Foundations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
07E - Lipstick	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
08E - Nail Polish and Enamel	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
08G - Other Manicuring Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
10A - Bath Soaps and Detergents	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	3
10B - Deodorants (underarm)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	4
10E - Other Personal Cleanliness Products	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
12A - Cleansing	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	6
12B - Depilatories	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
12C - Face and Neck (exc shave)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	6
12D - Body and Hand (exc shave)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	3
12F - Moisturizing	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	15
12H - Paste Masks (mud packs)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
12J - Other Skin Care Preps	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	8

01A - Baby Shampoos	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
01B - Baby Lotions, Oils, Powders, and Creams	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	4
01C - Other Baby Products	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	2
02A - Bath Oils, Tablets, and Salts	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	43
02B - Bubble Baths	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	6
02D - Other Bath Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	6
03D - Eye Lotion	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
03G - Other Eye Makeup Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
04A - Cologne and Toilet waters	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
04B - Perfumes	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
04E - Other Fragrance Preparation	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	14
05A - Hair Conditioner	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	15
05B - Hair Spray (aerosol fixatives)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
05E - Rinses (non-coloring)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
05F - Shampoos (non-coloring)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	25
05G - Tonics, Dressings, and Other Hair Grooming Aids	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	5
05H - Wave Sets	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
05I - Other Hair Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	2
06D - Hair Shampoos (coloring)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
07C - Foundations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
07I - Other Makeup Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
08E - Nail Polish and Enamel	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
08G - Other Manicuring Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
09A - Dentifrices	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	3
09C - Other Oral Hygiene Products	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
10A - Bath Soaps and Detergents	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	44
10B - Deodorants (underarm)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	3
10E - Other Personal Cleanliness Products	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	13
11B - Beard Softeners	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	3
11D - Preshave Lotions (all types)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	2
11E - Shaving Cream	EUCALYPTUS GLOBULUS	3

	(EUCALYPTUS) LEAF OIL	
11G - Other Shaving Preparation Products	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	9
12A - Cleansing	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	21
12C - Face and Neck (exc shave)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	18
12D - Body and Hand (exc shave)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	26
12E - Foot Powders and Sprays	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	7
12F - Moisturizing	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	53
12H - Paste Masks (mud packs)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	11
12I - Skin Fresheners	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	4
12J - Other Skin Care Preps	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	57
13B - Indoor Tanning Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
		414

12A - Cleansing	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF POWDER	2
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02A - Bath Oils, Tablets, and Salts	EUCALYPTUS	7
04B - Perfumes	EUCALYPTUS	5
04E - Other Fragrance Preparation	EUCALYPTUS	5
05G - Tonics, Dressings, and Other Hair Grooming Aids	EUCALYPTUS	1
08G - Other Manicuring Preparations	EUCALYPTUS	2
10A - Bath Soaps and Detergents	EUCALYPTUS	1
10E - Other Personal Cleanliness Products	EUCALYPTUS	1
12C - Face and Neck (exc shave)	EUCALYPTUS	2
12D - Body and Hand (exc shave)	EUCALYPTUS	6
12F - Moisturizing	EUCALYPTUS	1
12J - Other Skin Care Preps	EUCALYPTUS	10
		41

No uses were reported in the 2017 VCRP for:

Eucalyptus Globulus Leaf
 Eucalyptus Globulus Leaf/Twig Oil
 Eucalyptus Globulus Leaf Water



Memorandum

TO: Bart Heldreth, Ph.D., Executive Director
COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: September 29, 2017

SUBJECT: Concentration of Use by FDA Product Category: *Eucalyptus globulus*-Derived Ingredients

Concentration of Use by FDA Product Category – *Eucalyptus globulus*-Derived Ingredients*

Eucalyptus Globulus Leaf Oil
 Eucalyptus Globulus Leaf
 Eucalyptus Globulus Leaf Extract

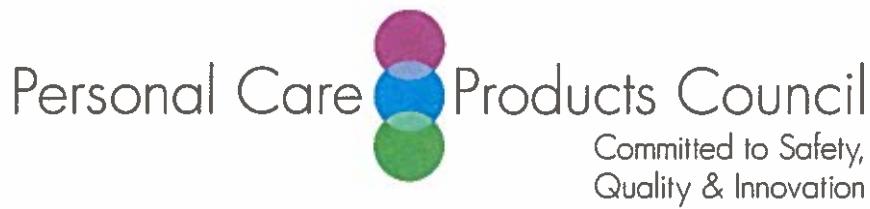
Eucalyptus Globulus Leaf Powder
 Eucalyptus Globulus Leaf/Twig Oil
 Eucalyptus Globulus Leaf Water

Ingredient	Product Category	Maximum Concentration of Use
Eucalyptus Globulus Leaf Oil	Baby shampoo	0.000019%
Eucalyptus Globulus Leaf Oil	Baby lotions, oils and creams Not powder	0.00067%
Eucalyptus Globulus Leaf Oil	Other baby products	0.000002%
Eucalyptus Globulus Leaf Oil	Bath oils, tablets and salts	0.13%
Eucalyptus Globulus Leaf Oil	Bubble baths	0.2%
Eucalyptus Globulus Leaf Oil	Eye shadows	0.00021%
Eucalyptus Globulus Leaf Oil	Eye lotions	0.038%
Eucalyptus Globulus Leaf Oil	Eye makeup removers	0.00001%
Eucalyptus Globulus Leaf Oil	Colognes and toilet waters	0.4%
Eucalyptus Globulus Leaf Oil	Other fragrance preparations	0.2%
Eucalyptus Globulus Leaf Oil	Hair conditioners	0.00001-0.011%
Eucalyptus Globulus Leaf Oil	Hair sprays Aerosol	0.002%
Eucalyptus Globulus Leaf Oil	Shampoos (noncoloring)	0.00001-0.12%
Eucalyptus Globulus Leaf Oil	Tonics, dressings and other hair grooming aids	0.0031-0.04%
Eucalyptus Globulus Leaf Oil	Hair dyes and colors	0.005%
Eucalyptus Globulus Leaf Oil	Foundations	0.001%
Eucalyptus Globulus Leaf Oil	Lipstick	0.008-0.35%
Eucalyptus Globulus Leaf Oil	Other makeup preparations	0.0001%
Eucalyptus Globulus Leaf Oil	Nail polish and enamel	0.0001%
Eucalyptus Globulus Leaf Oil	Other manicuring preparations	0.15%
Eucalyptus Globulus Leaf Oil	Mouth washes and breath fresheners	0.74%
Eucalyptus Globulus Leaf Oil	Bath soaps and detergents	0.00013-0.2%
Eucalyptus Globulus Leaf Oil	Aftershave lotions	0.0005%
Eucalyptus Globulus Leaf Oil	Preshave lotions	0.00015%
Eucalyptus Globulus Leaf Oil	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0001-0.1%
Eucalyptus Globulus Leaf Oil	Face and neck products Not spray Spray	0.098-0.27% 0.0008%
Eucalyptus Globulus Leaf Oil	Body and hand products Not spray	0.001-5.5%
Eucalyptus Globulus Leaf Oil	Moisturizing products Not spray	0.00071-0.2%
Eucalyptus Globulus Leaf Oil	Night products Spray	0.01%

Eucalyptus Globulus Leaf Oil	Paste masks and mud packs	0.00091-0.025%
Eucalyptus Globulus Leaf Oil	Skin fresheners	0.11%
Eucalyptus Globulus Leaf Oil	Other skin care preparations	0.00001-0.2%
Eucalyptus Globulus Leaf Oil	Suntan products Not spray Spray	0.00016-0.001% 0.00056%
Eucalyptus Globulus Leaf Oil	Indoor tanning preparations	0.00001%
Eucalyptus Globulus Leaf Oil	Other suntan preparations	0.001%
Eucalyptus Globulus Leaf	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1.2%
Eucalyptus Globulus Leaf Extract	Hair conditioners	0.0087%
Eucalyptus Globulus Leaf Extract	Hair sprays Aerosol	0.000006-0.005%
Eucalyptus Globulus Leaf Extract	Shampoos (noncoloring)	0.000008-0.005%
Eucalyptus Globulus Leaf Extract	Tonics, dressings and other hair grooming aids	0.00021%
Eucalyptus Globulus Leaf Extract	Foundations	0.001%
Eucalyptus Globulus Leaf Extract	Dentifrices	0.41%
Eucalyptus Globulus Leaf Extract	Mouth washes and breath fresheners	0.058%
Eucalyptus Globulus Leaf Extract	Bath soaps and detergents	0.015-0.025%
Eucalyptus Globulus Leaf Extract	Shaving cream	0.00048-0.00053%
Eucalyptus Globulus Leaf Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0015%
Eucalyptus Globulus Leaf Extract	Face and neck products Not spray	0.005%
Eucalyptus Globulus Leaf Extract	Paste masks and mud packs	0.01%
Eucalyptus Globulus Leaf Extract	Other skin care preparations Rinse-off	0.0003-0.01%
Eucalyptus Globulus Leaf Extract	Indoor tanning preparations	0.00005%
Eucalyptus Globulus Leaf Powder	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1%
Eucalyptus Globulus Leaf Water	Hair conditioners	0.02%
Eucalyptus Globulus Leaf Water	Shampoos (coloring)	0.1%
Eucalyptus Globulus Leaf Water	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.002%
Eucalyptus Globulus Leaf Water	Face and neck products Not spray	1.4%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2017
Table prepared: September 29, 2017



Memorandum

TO: Bart Heldreth, P.h.D., Executive Director
COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 27, 2017

SUBJECT: Eucalyptus Globulus Leaf Oil

Anonymous. 2011. Certificate of analysis Australian Eucalyptus Oil.

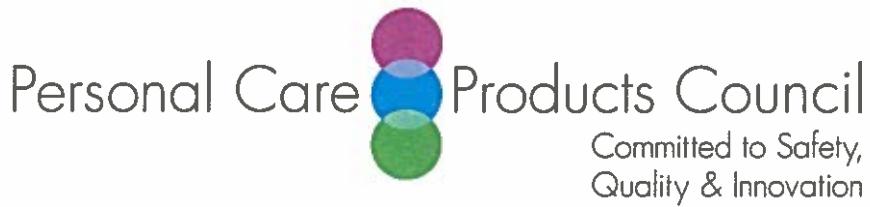
CERTIFICATE OF ANALYSIS

Australian Eucalyptus Oil

Certification date: June 2011
Batch No: 110109-1
Standard Name: Eucalyptus Oil
Botanical Name: *Eucalyptus globulus*
INCI Name: Eucalyptus globulus oil
Appearance: Pale yellow mobile liquid
Odour: Fresh, reminding of cineol
Country of Origin: Australia
Part of Plant Used: Leaves
Extraction Method: Steam Distilled
Specific Gravity @ 20°C: 0.907
Refractive Index @ 20°C: 1.4611

Test	Result
α- pinene %	1.2,
β- pinene %	0.6
α- phellandrene %	1.0
Limonene %	7.7
β -phellandrene %	0.3
p-cymene %	3.2
1,8 cineole %	78.8
γ – terpinen %	4.4
terpinen-4-ol%	0.2
α-terpineol %	0.3
camphor %	0.0

Date of Manufacture: January 2011
Date of Expiry: January 2014



Memorandum

TO: Bart Heldreth, P.h.D.
Executive Director, Cosmetic Ingredient Review(CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 30, 2017

SUBJECT: Scientific Literature Review: Safety Assessment of *Eucalyptus globulus* (Eucalyptus)-Derived Ingredients as Used in Cosmetics (SLR posted on CIR's website October 5, 2017)

The Council has no suppliers listed for Eucalyptus Leaf and Eucalyptus Leaf Powder.

Key Issues

In many headings in the report it states: "equivalence to cosmetic material is not confirmed", when the composition of the material tested is not clearly stated in the SLR. How well tested materials represent cosmetic ingredients is always an issue for CIR reports. The material(s) considered safe are those that are the same or similar to the materials that were tested. In this case, all references appear to agree that Eucalyptus Globulus Leaf Oil primarily consists of 1,8-cineole (eucalyptol). Why would a cosmetic ingredient differ from this composition? Additional references for composition cited in Tisserand and Young (2014) (reference 24 in the SLR) but not cited in the CIR report are:

- Lawrence BM. 1989. Essential oils 1981-1987. Allured Publishing, Wheaton. p. 199-200.
- Lawrence BM. 1993. Essential oils 1988-1991. Allured Publishing, Wheaton. p. 122-125.

These references indicate that Eucalyptus Globulus Leaf Oil contains 65.4-83.9% 1,8-cineole. Tissarand and Young (2014) also provide information on which other species of *Eucalyptus* have leaf essential oils that contain high levels of 1,8-cineole.

It should also be noted that Eucalyptus Leaf and Eucalyptus Oil are included in the *British Pharmacopoeia* (2008 edition in Joyce's office). According to this reference, the main species used to produce the oil are *Eucalyptus globulus*, *Eucalyptus polybractea* and *Eucalyptus smithii*. The oil must contain a minimum of 70% 1,8-cineole.

It would be helpful to add the use recommendations by Tisserand and Young (2014) to the CIR report:

Maximum adult daily oral dose: 600 mg

Maximum dermal use level: 20%

Hazards: "Essential oils high in 1,8-cineole can cause CNS and breathing problems in young children."

Contraindications: "Do not apply to or near the face of infants or children under ten years of age."

As there is no information on phototoxicity in the SLR, the *in vitro* study¹ cited in Tisserand and Young (2014) should be added to the report.

Additional Considerations

Introduction - As reference 25 and 26 appear to concern quercetin, in it not clear why they are include with a sentence about geraniol.

Definition and Structure - This section implies that the CAS numbers may not be correct for the INCI names. This has been brought to the attention of Joanne Nikitakis. The generic number 84625-32-1, is likely appropriate for all of the ingredients in the report.

Definition and Structure, Plant Identification - Is it necessary for both of these sections to state that the genus "contains more than 750 species"?

Composition/Constituents - Please provide a reference for the following sentence: "Another author reported that fresh leaves of *Eucalyptus globulus* contain only 1.87% volatile oil with 35.7% 1,8-cineole."

Penetration Enhancement - In the study of TMP in rat and human skin with three concentrations of Eucalyptus Globulus Leaf Oil (reference 36), only three enhancement ratios are stated, which are presumably respective to the three concentrations tested. Are these values for rats or humans, or for both species? What was the receptor fluid used in this study?

Short-Term - Please correct "rote"

What was the duration of the rat study cited to reference 44?

It is not necessary to state the dose (130 mg dry leaves/kg) twice in the description of reference 45.

The following is not a complete sentence: "RBC counts (-17.1 below control level) at 10th dose."

Please correct: "repertory rates"

Sensitization - As there are some multicenter studies concerning sensitization in the Clinical Studies section, it is not appropriate to state that no sensitization studies were found. It should state that the only studies concerning sensitization that were found were patch test

¹Placzek M, Frömel W, Eberlein B, et al. 2007. Evaluation of phototoxic properties of fragrances. *Acta Derm Venereol* 87: 312-316.

studies of dermatologic patients.

Retrospective and Multicenter, Table 13 - It is not correct to call the multicenter patch test studies of dermatologic patients "retrospective" a term used to describe a specific type of epidemiology study. "A retrospective study looks backwards and examines exposures to suspected risk or protection factors in relation to an outcome that is established at the start of the study."

Summary - Please correct: "for Eucalyptus Globulus Leaf Oil was 3320 mg/kg Eucalyptus Globulus Leaf Oil..."

Please correct: "Rabbits inhaling steam..... containing Eucalyptus Globulus Leaf Oil caused deaths..." (presumably in was the eucalyptus oil they inhaled that caused the deaths - not the rabbits).

Please correct: "Eucalyptus Globulus Leaf Oil inadvertently given intranasally to has caused irritated nasal mucous membranes."

It should be made clear that the hyaline droplet nephropathy was observed in male rats.

Table 3 - Did the authors of reference 41 really use "flowers" in the preparation of Eucalyptus Globulus Leaf Oil? Or were flowers used for some other type of essential oil (clove) examined in this reference?

Table 4 - Was there any indication of the detection limits used to determine the presence or absence of the various components of *Eucalyptus globulus* ingredients?

Table 8 - Although hops essential oil contains β -myrcene, are references 69 and 70 really the most appropriate references to support that β -myrcene is a potential irritant and could cause asthma-like symptoms? Citing a RIFM sponsored study², Tisserand and Young (2014) state β -myrcene was not an irritant or a sensitizer when tested in 25 volunteers.

What is the basis for the suggestion that phellandrene is a potential carcinogen?

Tisserand and Young (2014) cite Roe and Field (1965) (reference 46 in the SLR) and state: " α -Phellandrene has been reported to promote tumor formation on the skin of mice treated with the primary carcinogen DMBA, but is not carcinogenic in its own right."

Table 11 - It is not clear why the first column includes the statement "plant part and solvent not specified" for Eucalyptus Globulus Leaf Oil which is made from leaves using hydrodistillation (see Table 3) or steam distillation.

Table 14 - As this table includes more than "ingestion" studies, the title of the table needs to be corrected.

Please correct: "He spoke rationally several times up less than an hour of his death."

²Opdyke DLJ. 1976. Monographs on fragrance raw materials. *Fd Cosmet Toxicol* 14(suppl.) p. 615.