Check for updates

International Journal of Toxicology
2023, Vol. 42 (Supplement 1) 57S–92S
© The Author(s) 2023
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/10915818231164354
journals.sagepub.com/home/ijt
SAGE

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

Lillian C. Becker*, Alice Akinsulie*, Wilma F. Bergfeld, Donald V. Belsito**, Ronald A. Hill***, Curtis D. Klaassen**, Daniel C. Liebler***, James G. Marks***, Ronald C. Shank***, Thomas J. Slaga**, Paul W. Snyder**, and Bart Heldreth†**

Abstract

This is a safety assessment of 6 *Eucalyptus globulus* (eucalyptus)-derived ingredients as used in cosmetics. The reported functions of the *Eucalyptus globulus* (eucalyptus)-derived ingredients include abrasive, fragrance ingredient, and skin-conditioning agent (miscellaneous and occlusive). The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the relevant data on these ingredients. Because final product formulations may contain multiple botanicals, each containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. Industry should use good manufacturing practices to limit impurities. The Panel concluded that *Eucalyptus globulus* (eucalyptus)-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing.

Keywords

eucalyptus, cosmetics, safety

Introduction

This is a safety assessment 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
Eucalyptus Globulus Leaf Extract
Eucalyptus Globulus Leaf Oil
Eucalyptus Globulus Leaf Powder
Eucalyptus Globulus Leaf/Twig Oil
Eucalyptus Globulus Leaf Water

To avoid redundancy of effort, the Cosmetic Ingredient Review (CIR) may exclude from review ingredients that are known to exclusively function as fragrance ingredients when the ingredient has been or will be evaluated by the Research Institute for Fragrance Materials (RIFM). According to the *Dictionary*, Eucalyptus Globulus Leaf/Twig Oil and Eucalyptus Globulus Leaf Water are only reported to function as fragrance ingredients.[1] However, communications with RIFM in November 2017 revealed that these ingredients have neither been assessed for safety by the RIFM Expert Panel, nor are these ingredients on RIFM's prioritized agenda to be reviewed in the foreseeable future. Thus, the Panel is reviewing the safety of these ingredients as part of this assessment.

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 senisitzer.[2-6] In this safety assessment, the Panel is reviewing information available to evaluate the

*Cosmetic Ingredient Review Scientific Former Analyst/Writer
**Expert Panel for Cosmetic Ingredient Safety Member
***Expert Panel for Cosmetic Ingredient Safety Former Member
†Cosmetic Ingredient Review Executive Director

Corresponding Author:
Please address correspondence to Bart Heldreth, Executive Director, Cosmetic Ingredient Review, 1620 L Street, NW, Suite 1200, Washington, DC 20036, USA.
Email: cirinfo@cir-safety.org

Table 1. Definitions and Reported 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 *Eucalyptus globulus* and other species of *Eucalyptus*	Fragrance ingredient; skin-conditioning agent - miscellaneous
Eucalyptus globulus leaf	Eucalyptus globulus leaf [is] the leaves of *Eucalyptus globulus*	Skin-conditioning agent - miscellaneous
Eucalyptus globulus leaf extract 84625-32-1	Eucalyptus globulus leaf extract is the extract of the leaves of *Eucalyptus globulus*	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 *Eucalyptus globulus*	Abrasive
Eucalyptus globulus leaf/Twig oil	Eucalyptus globulus leaf/Twig oil is the volatile oil obtained from the leaves and twigs of *Eucalyptus globulus*	Fragrance ingredient
Eucalyptus globulus leaf water	Eucalyptus globulus leaf water is an aqueous solution of the steam distillate obtained from the leaves of *Eucalyptus globulus*	Fragrance ingredient

potential toxicity of each of the *Eucalyptus globulus*-derived ingredients as whole, complex mixtures. Except for specific constituents of concern, the Panel is not reviewing information that may be available to assess the potential toxicity of the individual constituents derived from *Eucalyptus globulus*. However, Eucalyptus Globulus Leaf Oil consists of not less than 70% (w/w) eucalyptol (also known as cineol, cineole, or 1,8-cineole), a cosmetic ingredient that has not been reviewed by the Panel.[1,7] Since the content of eucalyptol is so high, it is appropriate to include relevant toxicity data on eucalyptol as supporting information for the *Eucalyptus globulus* (eucalyptus)-derived ingredients. Representative data are summarized in the relevant sections in this safety assessment. While the data are being considered in evaluating the safety of *Eucalyptus globulus* (eucalyptus)-derived ingredients, the safety of eucalyptol as used in cosmetics is not being assessed in this report.

The 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.[8] The Panel reviewed the safety of phytosterols, which are plant-derived sterols, in 2013 and concluded that the phytosterol cosmetic ingredients are safe as used.[9]

The names of the cosmetic ingredients in this report are written in accordance with the International Nomenclature Cosmetic Ingredient (INCI) naming conventions as shown above, i.e., 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*). 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 INCI name is used.

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 the Panel typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics and chemicals industries, as well as by other interested parties.

Some of the data included in this safety assessment were found on the European Chemicals Agency (ECHA)[10] and the International Program of Chemical Safety (INCHEM)[11] websites. In this safety assessment, ECHA and INCHEM are cited as the references for summaries of information obtained from these websites. Also referenced in this safety assessment are summary data found in reports made publicly available by the World Health Organization (WHO)[7] and the European Medicines Agency (EMA) Products Committee on Herbal Medicinal Products (HMPC).[12]

Chemistry

Definition

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*, etc.) 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*. The *Dictionary* defines Eucalyptus Globulus Leaf Oil as the volatile oil obtained from the leaves of *Eucalyptus*

globulus and other species of *Eucalyptus*. "Eucalyptus oil" may be extracted from any *Eucalyptus* species that is rich in eucalyptol.[7] The other main species that *Eucalyptus* essential oil is extracted from are *Eucalyptus polybractea* and *Eucalyptus smithii*, which contain a minimum of 70% eucalyptol.[15]

In addition, according to the *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 *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.[7,12]

Eucalyptus globulus is a large tree with smooth, very pale or ash-grey bark, which grows up to 20 m high.[7,12,16-20] 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, eucalyptol 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) in length, 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 eucalyptol, minty, and camphoraceous. At 2 to 8 h, the odor is hay- and cumic-like, similar to rosemary. At 5 to 20 h, the odor is woody, dusty, and powdery. The specific gravity of Eucalyptus Globulus Leaf Oil and Eucalyptus Globulus Leaf/Twig Oil increases as the eucalyptol content increases (.9005 to .930).[21]

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 to ECHA (Table 4).[10] The constituents in these ingredients include eucalyptol, pin-2(10)-ene, dipentene, and (*R*)-*p*-mentha-1,8-diene. Eucalyptol, the most common constituent, with the highest concentration, is shown in Figure 1.

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) eucalyptol.[7] Another report states that fresh leaves of *Eucalyptus globulus* contained 54% to 61% eucalyptol, 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% eucalyptol.[12]

Phytosterols were found in chloroform and methanol extracts of *Eucalyptus globulus* leaves but not in petroleum ether or aqueous extracts.[8] Table 5 shows the major constituent groups found by using different extract media.

Table 2. Chemical Properties of *Eucalyptus globulus*-Derived Ingredients.

Property	Value	Reference
Eucalyptus globulus leaf		
Odor	Aromatic, camphoric	7
Eucalyptus globulus leaf extract		
Physical form	Liquid	37
Color	Light to medium amber	37
Odor	Characteristic	37
Specific gravity (@ 25°C)	.99 - 1.01	37
Water solubility	Soluble	37
Eucalyptus globulus (eucalyptus) leaf oil		
Physical form	Liquid/oil	11
	Liquid	10
Color	Colorless to pale yellow	11
	Clear, yellow to pale yellow	10
Specific gravity (@ 25°C)	.913 – .92	10
(@ 20°C)	.909	10
Melting point (°C)	< −20	10
Boiling point (°C)	153 – 184	10
Water solubility	Insoluble	11
Other solubility		
Alcohol (70%)	Soluble	11
Alcohol (90%)	Miscible	11
Eucalyptus globulus leaf/Twig oil		
Physical form	Liquid	7
Color	Colorless or pale yellow	7
Odor	Aromatic, camporic	7
Other solubility		
Ethanol	Soluble	7

Table 3. Methods of Manufacture Reported in the Literature.

Ingredient	Method	Reference
Eucalyptus globulus leaf oil	Freshly collected *Eucalyptus* leaves were cleaned by using distilled water and air-dried at room temperature under shade. The leaves were then chopped into small pieces and essential oil extraction accomplished by hydro-distillation in a modified clevenger-type apparatus. The oil was filtered and concentrated using rotary evaporator	57
Eucalyptus globulus leaf oil	*Eucalyptus globulus* 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	59
Eucalyptus globulus leaf oil	Eucalyptus globulus leaf oil used for medicinal purposes is manufactured from fresh leaves or fresh terminal branchlets of *Eucalyptus globulus* plants. Oil is extracted by steam distillation and retification	12
Eucalyptus globulus leaf extract	Freshly collected *Eucalyptus globulus* 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	62
Eucalyptus globulus leaf extract	Freshly collected *Eucalyptus globulus* leaves were air-dried followed by milling into a powder. The powder (200 g) was then percolated in distilled water (500 mL) for 2 w. The percolated mixture was filtered and evaporated on a water bath	63
Eucalyptus globulus leaf extract	The extract was prepared by powdering *Eucalyptus globulus* 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%	64
Eucalyptus globulus leaf extract	Fresh or dried leaves are extracted with specified eluent(s) at specified temperature (not specified) to yield a concentrate. Concentrate is then blended with desired diluent(s) and preservation system to product the final product	37

Table 4. Constituents of *Eucalyptus globulus*-Derived Ingredient Reported to the ECHA Database From Various Suppliers (Concentrations Were Not provided).[10]

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

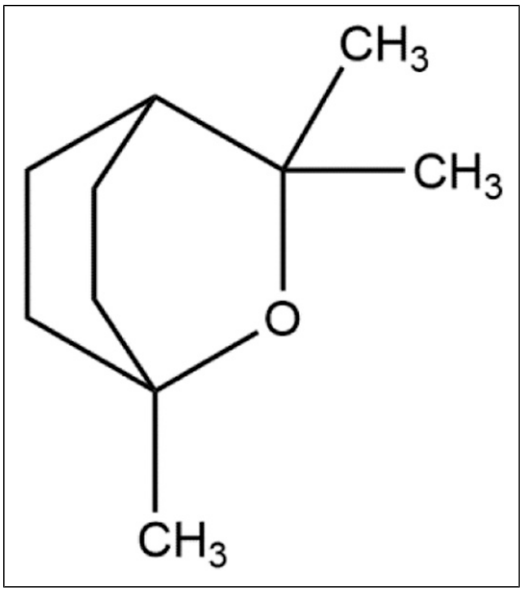

Figure 1. Reported primary component of *Eucalyptus*, eucalyptol.

Eucalyptus Globulus Leaf Extract. A supplier reports that the aqueous Eucalyptus Globulus Leaf Extract contains no eucalyptol.[22]

Eucalyptus Globulus Leaf Oil. A supplier reported the constituents of Eucalyptus Globulus Leaf Oil, which included eucalyptol at 78.8% (Table 6). Another source reported on the concentration ranges of the constituents of Eucalyptus Globulus Leaf Oil (essential oil; Table 7). As shown in Table 8, 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.[20,23,24]

Eucalyptus Globulus Leaf/Twig Oil. In general, the major constituent of Eucalyptus Globulus Leaf/Twig Oil is eucalyptol (54% to 95%).[7] In addition, there are reported to be 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) eucalyptol. Eucalyptus Globulus Leaf/Twig Oil also contains monoterpenes such as β-pinene, limonene, geraniol and camphene.[12]

Constituents of Concern. Constituents of the *Eucalyptus globulus* plant that may be of concern are listed in Table 9.

Potential sensitizers include geraniol[2-6] (found in the essential oil) and the hydroperoxides of limonene[2,6,25] (leaf essential oil) and linalool[2,26] (leaf and leaf essential oil).[27]

Other constituents of concern found in the *Eucalyptus globulus* plant are myrcene (leaf essential oil), pinene

Table 5. Constituent Groups Found in *Eucalyptus globulus* Leaf Extracts Using Different Extract Mediums.[8]

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

Table 6. The Constituents of Eucalyptus Globulus Leaf Oil Reported by a Supplier.[91]

Constituent	Content (%)
Camphor	0.0
Eucalyptol	78.8
Limonene	7.7
p-Cymene	3.2
Terpinen-4-ol	0.2
α-Phellandrene	1.0
α-Pinene	1.2
α-Terpineol	0.3
β-Phellandrene	0.3
β-Pinene	0.6
γ-Terpinen	4.4

Table 7. The Variability of Constituent Percentages of Eucalyptus Globulus Leaf Oil (Essential Oil) at 1% or Greater.[6]

Constituent	Content (%)
(+)-Aromadendrene	1.2 – 3.5
(+)-limonene	1.8 – 9.0
(*E*)-Pinocarveol	2.3 – 4.4
Eucalyptol	65.4 – 83.9
Globulol	Trace – 5.3
p-Cymene	1.2 - 3.5
Pinocarvone	Trace – 1.0
α-Pinene	3.7 – 14.7

(essential oil, leaf, and leaf essential oil) and quercetin (leaf and stem bark).[27] These constituents are potential carcinogens or are genotoxic.[28-30,30-33]

The International Fragrance Association (IFRA) publishes restrictions for fragrance ingredients, which form the basis for the globally accepted and recognized risk management system for the safe use of fragrance ingredients.[34] Constituents of *Eucalyptus globulus* leaves and oil that have restrictions established by the International Fragrance Association Standards are listed in Table 10.

Impurities

A supplier reported specifications for a trade name mixture containing 10% Eucalyptus Globulus Leaf Extract include a total bacterial count limit of < 100 colony forming units (cfu)/g.[35] This supplier also reported specifications for this same trade name mixture that certain allergens, including eugenol, geraniol, and linalool, are not detected (limit of detection .001%; Table 11).[36]

Another supplier reported specifications for another trade name mixture containing Eucalyptus Globulus Leaf Extract (concentration not specified; Table 11).[37] This mixture was also reported to not contain allergens and not to contain antimony (detection limit .021 gm/L), arsenic (.055 mg/L), cadmium (.004 mg/L), chromium (.010 mg/L) iron (.087 mg/L), lead (.015 mg/L), mercury (.0002 mg/L) or nickel (.016 mg/L). There were no residual pesticides detected and a total bacterial count limit of < 100 organisms/g (opg).

Use

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the US 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 2018, Eucalyptus Globulus Leaf Oil is reported to be used in 433 formulations (214 leave-on formulations, 160 rinse-off formulations, and 59 formulations that are diluted for the bath).[38] Eucalyptus Globulus Leaf Extract is reported to be used in 77 formulations and Eucalyptus Globulus Leaf Powder is reported to be used in 2 formulations. The VCRP included ingredients with the non-INCI name "eucalyptus" (42 reported uses) and "eucalyptus extract" (11 reported uses; Table 12).

Table 8. Comparison of Chemical Composition of the Essential Oil From *Eucalyptus globulus* Leaves Collected From Different Locations Extracted by Steam Distillation.[20,23,24]

Compounds	Algeria (%)	China (%)	Northern Ethiopia (%)
4-Terpineol	.178	*	*
Alloaromadendrene	*	2.47	*
Aromadendrene	*	*	.694-2.858
Borneol	.346	*	*
Camphene	.117	*	.164-.269
Caren-4-ol	.195	*	*
cis-Carveol	.187	*	*
cis-Ocimene	*	*	15.923-21.331
Eucalyptol	51.083	72.71	66.283-75.361
Fenchol	.179	*	*
Globulol	2.817	2.77	.819-1.431
L-pinocarveol	9.987	*	*
Myrtenol	.202	*	*
α-Campholenal	.390	*	*
α-pinene	24.600	9.22	*
α-Terpineol	.486	2.54	1.505-2.256
α-Terpineol acetate	1.2	3.11	2.188-3.391
β-Myrcene	*	*	.658-1.004
β-pinene	.217	*	.957-1.237
Total identified	**92.184**	**92.82**	**89.191-109.138**

* Not found or found at <1%.

Table 9. Constituents of the *Eucalyptus globulus* Plant That May be of Concern.

Constituent	Concern	References
Geraniol	Potential dermal sensitizer	2-6
Limonene	Hydroperoxides are potential dermal sensitizers	2,6,25
Linalool	Hydroperoxides are potential dermal sensitizers. Safe at up to 4.3% (20% in a consumer fragrance)	2,26
Quercetin	Positive genotoxic effect in an Ames assay Consistently genotoxic in in vitro tests and in some in vivo studies of i.p. exposures, but was consistently non-genotoxic in oral exposure studies	32,33
β-Myrcene	Oral dosing for 2 years caused kidney cancers in male rats (.25 g/kg) and liver cancer in male mice (.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	28
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	30,31

The results of a concentration of use survey conducted by the Council in 2017, and revised in 2018, indicate Eucalyptus Globulus Leaf Water is used at up to 1.4%, with the maximum use reported in face and neck products.[39] The rest of the ingredients with reported concentrations of use are used at a maximum of .4% in leave-on products or 1.2% in rinse-off products.

In some cases, no uses were reported in the VCRP, but concentration of use data were received from industry. For instance, although Eucalyptus Globulus Leaf Water has concentrations of use reported in several categories, there are no reported uses in the VCRP. It should be presumed there is at least one use in every category for which a concentration is reported.

One *Eucalyptus globulus*-derived ingredient, Eucalyptus Globulus Leaf/Twig Oil, had no uses reported in the VCRP or industry survey.

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 .038% Eucalyptus Globulus Leaf Oil), and in products that may be ingested and come in contact with mucus membranes (e.g., mouthwashes and breath fresheners

Table 10. Constituents of *Eucalyptus globulus* Leaves and Oil That Have IFRA Standards.[34]

Constituent	Standard Limits
2-Phenylacetaldehyde	Limited to .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 .17% - 5%, depending on use category due to sensitization.*
Carvone	Limited to .08% - 5%, depending on use category due to sensitization.*
Citronellol	Limited to .8% - 21.4%, depending on use category due to sensitization.*
Cuminaldehyde	Limited to .03% - 5%, depending on use category due to sensitization.*
trans-β-Damascenone	Limited to .2% in fragrances and Eau de Toilette; .01% in other leave-on and rinse-off products; and .2% in non-skin, and incidental skin contact products due to carcinogenicity
Estragol	Limited to .2% - 4.3%, depending on use category due to sensitization.*
Eugenol	Limited to .2% - 4.3%, depending on use category due to sensitization.*
Geraniol	Limited to .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	D-, L-and DL-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 .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 .02% - 3%, depending on use category due to sensitization.*

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

at up to .74% Eucalyptus Globulus Leaf Oil). Eucalyptus Globulus Leaf Oil is reported to be used in baby products at up to .00067%.

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 .4% and hair sprays at up to .002%. In practice, most 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.[40,41] 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.[42,43]

The cosmetic ingredient SD alcohol 38-B may be denatured with any of several essential oils, including *Eucalyptus globulus* oil.[1] Essential oils used as a denaturant must meet National Formulary (NF) specifications. [27 CFR 21.92] Specifications for eucalyptol (there are no specific standards for *Eucalyptus globulus* oil) include a specific gravity between .921 and .924, congealing temperature ≥ 0, distilling temperature range between 174 and 177°C, and no detectable phenols.[44]

The FDA lists "*Eucalyptus globulus*" as a non-traditional preservative for cosmetics in its Compliance Program Guidance Manual.[45]

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.[46]

Non-Cosmetic

Food. In the US, *Eucalyptus globulus* is not generally used for human food, but as an additive. *Eucalyptus globulus* (*Eucalyptus globulus* Labill) leaves are food additives permitted for direct addition to food for human consumption as a flavoring agent. [21 CFR 172.510] 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.[17]

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 when used at 2 g or less *Eucalyptus globulus* oil per hive, where the eucalyptus oil contains 80% or more eucalyptol. [40 CFR 180.1271]

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil). The European Commission Scientific Committee on Food (SCF) concluded that the available toxicological studies of eucalyptol are limited and inadequate to derive an acceptable daily intake (ADI).[47] However, the available animal data do not indicate a cause of concern associated with the daily intake

Table 11. Allergens[a] That are Specified to Not be Detected in Trade Name Mixtures Containing *Eucalyptus Globulus* Leaf Extract (Detection Limit .001%).[36,37]

Allergen	Trade name mixture Containing Eucalyptus Globulus Leaf Extract at 10%	Trade name mixture Containing Eucalyptus Globulus Leaf Extract at Unspecified Concentration
Amyl cinnamal	Not detected	Not detected
Amyl cinnamal alcohol	Not detected	Not detected
Anise alcohol	Not detected	Not detected
Benzyl alcohol	Not detected	Not detected
Benzyl benzoate	Not detected	Not detected
Benzyl cinnamate	Not detected	Not detected
Benzyl salicylate	Not detected	Not detected
Butylphenyl metahylpropional	Not detected	Not detected
Cinnamal	Not detected	Not detected
Cinnamyl alcohol	Not detected	Not detected
Citral	Not detected	Not detected
Citronellol	Not detected	Not detected
Coumarin	Not detected	Not detected
Eugenol	Not detected	Not detected
Farnesol	Not detected	Not detected
Geraniol	Not detected	Not detected
Hexyl cinnamal	Not detected	Not detected
Hydroxycitronellal	Not detected	Not detected
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	Not detected	Not detected
Isoeugenol	Not detected	Not detected
α-Isomethyl ionone	Not detected	Not detected
Limonene	Not tested	Not detected
D-Limonene	Not detected	Not tested
Linalool	Not detected	Not detected
Methyl 2-octynoate	Not detected	Not tested
Methyl 12-octynoate	Not tested	Not detected

[a]The 26 fragrance allergens defined by the seventh Amendment of the Scientific Committee on Cosmetic and Non-Food Products (SCCNFP) Allergens Annex III.

from food, estimated from the small amount of information available.

Drugs. *Eucalyptus globulus* oil may be used in over-the-counter (OTC) products that treat nasal decongestion (in a lozenge or mouthwash), sinusitis, dermal irritation, fever blisters/cold sores, and poison ivy, oak and sumac, and in astringent and external analgesic 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 (1.2 to 1.3%) is permitted in combinations containing nasal decongestant and an analgesic-antipyretic. [21 CFR 341.40]

Combinations containing camphor, menthol, and *Eucalyptus globulus* oil are permitted for use as active ingredients in cold, cough, allergy, bronchodilator, and anti-asthmatic OTC drugs when so labeled. [21 CFR 341.85]

Eucalyptus globulus oil has been used in OTC smoking deterrents, but there is a lack of adequate data to establish general recognition of the safety and effectiveness. [21 CFR 310.544]

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.[7] 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 of eucalyptus oil obtained by steam distillation range from .3 to .6 mL essential oil or equivalent preparations.[7] Examples of oral dosages include: one capsule of 100 to 200 mg, 2 to 5 times daily; one lozenge of .2 to 15.0 mg dissolved slowly in the mouth, every 30 to 60 min; and a mouthwash as 20 mL of a .91 mg/mL solution, gargled twice daily. The dose for administration by inhalation is 12 drops *Eucalyptus globulus* oil/150 mL boiling water. For dermal use, daily dosage

Table 12. Frequency of Use According to Duration and Exposure of *Eucalyptus globulus*-Derived Ingredients.[38,39]

	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
Use Type	Eucalyptus Globulus Leaf Oil		Eucalyptus Globulus Leaf		Eucalyptus Globulus Leaf Extract		Eucalyptus Globulus Leaf Powder	
Total/range	433	.000002-.74	NR	1.2	77	.000006-.41	2	1
Duration of use[a]								
Leave-on	214	.000002-0.4	NR	NR	52	.000006-.005	NR	NR
Rinse-off	160	.00001-.74	NR	1.2	22	.000008-.41	2	1
Diluted for (bath) use	59	.13-0.2	NR	NR	3	NR	NR	NR
Exposure type								
Eye area	2	.00001-.038	NR	NR	2	NR	NR	NR
Incidental ingestion	7	.008-.74	NR	NR	1	.058-.41	NR	NR
Incidental inhalation-sprays	18; 73[a]; 48[b]	.00056-.4; .00001-.74[a]	NR	NR	16[a]; 10[b]	.000006-.005; .00005-.058[a]	NR	NR
Incidental inhalation-powders	4[c]; 48[b]	.001-.27[c]	NR	NR	1; 10[b]	.005[c]	NR	NR
Dermal contact	368	.000002-0.4	NR	1.2	57	.00005-.025	2	1
Deodorant (underarm)	3[a]	NR	NR	NR	4[a]	NR	NR	NR
Hair-noncoloring	55	.00001-.12	NR	NR	17	.000006-.0087	NR	NR
Hair-coloring	1	.005	NR	NR	NR	NR	NR	NR
Nail	2	.0001-.15	NR	NR	2	NR	NR	NR
Mucous membrane	131	.00013-.74	NR	NR	8	.015-.41	NR	NR
Baby	7	.000002-.00067	NR	NR	NR	NR	NR	NR
	Eucalyptus globulus leaf water		"Eucalyptus"		"Eucalyptus extract"[d]			
Total/range	NR	.02-1.4	42	NS	11	NS		
Duration of use								
Leave-on	NR	1.4	32	NS	6	NS		
Rinse-off	NR	.02-0.1	3	NS	5	NS		
Diluted for (bath) use	NR	NR	7	NS	NR	NS		
Exposure type								
Eye area	NR	NR	NR	NS	NR	NS		
Incidental ingestion	NR	NR	NR	NS	NR	NS		
Incidental inhalation-sprays	NR	NR	10; 2[a]; 8[b]	NS	4[a]; 1[b]	NS		
Incidental inhalation-powders	NR	1.4[c]	8[b]	NS	1[b]	NS		
Dermal contact	NR	.02-1.4	40	NS	10	NS		
Deodorant (underarm)	NR	NR	NR	NS	NR	NS		
Hair-noncoloring	NR	.02-0.1	2	NS	1	NS		
Hair-coloring	NR	NR	NR	NS	NR	NS		

(continued)

Table 12. (continued)

Use Type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Eucalyptus Globulus Leaf Oil		Eucalyptus Globulus Leaf		Eucalyptus Globulus Leaf Extract		Eucalyptus Globulus Leaf Powder	
Nail	NR	NR	NR	NS	NR	NS		
Mucous membrane	NR	NR	9	NS	3	NS		
Baby	NR	NR	NR	NS	1	NS		

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. NR = Not Reported; NS = Not Surveyed; Totals = Rinse-off + Leave-on + Diluted for Bath Product 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" and "eucalyptus extract" are not INCI names but were reported in the VCRP. It is not known if these correspond to cosmetic ingredients in this report.

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 yr of age and the cutaneous use should be limited to children over 4 yr 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] It is noted that essential oils high in eucalyptol 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 10 years of age.

Health Canada restricts the use of *Eucalyptus globulus* leaf essential oil to 1% to 5% for use as a massage oil (covering more than 10% of the body surface), but may be used up to 25% for a local (less than 10% of the body surface) use.[48] The oil may also be used in aromatherapy to help relieve joint/muscle pain associated with sprain/strain/rheumatoid arthritis, to help relieve headache, and to help relieve colds/cough.

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil). Eucalyptol may be used in lozenges and mouthwash that act as nasal decongestants, expectorants, dandruff/seborrheic dermatitis/psoriasis drug products, and oral care products. Based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these preparations for the specified uses. [21 CFR 310.545]

Other. *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]

Toxicokinetic Studies

Obtaining data on the toxicokinetics of unknown, complex mixtures, such as botanicals, would be impractical. However, if the compositions are well understood, including the concentrations of constituents, such studies may be useful.

Penetration Enhancement

In Vitro. In vitro dermal penetration enhancement studies of Eucalyptus Globulus Leaf Oil are summarized in Table 13.

Generally, dermal penetration of chlorhexidine digluconate (CHG) through human skin samples over 24 h increased in a manner dependent on the concentration of Eucalyptus Globulus Leaf Oil.[49] Eucalyptus Globulus Leaf Oil (82.9% eucalyptol) 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 for human skin were 3.38, 4.47, and 4.64, respectively.[50] 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% eucalyptol) to enhance the dermal penetration of ketorolac was evaluated using a dermal patch across abdominal rat skin, the

Table 13. Dermal Penetration Enhancement Studies of Eucalyptus Globulus Leaf Oil.

Ingredient/Substance	Drug	Details	Results	Reference
Eucalyptus globulus leaf oil (82.9% eucalyptol) tested at 0, 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 (5%, 10%, 20% and 50%v/v) and isopropyl alcohol (70% v/v) and distilled water. Mixtures without CHG were used as controls. Polysorbate 80 (.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	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. Combining 10% eucalyptus globulus leaf oil and CHG in 70% isopropyl alcohol significantly enhanced CHG dermal penetration compared to CHG and isopropyl alcohol .121 ±.019 vs .023 ± .007 μg/mg in upper 100 μm of skin. 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 .019 and .043 μg/mg tissue. At 30 min, concentration of CHG in upper 100 μm was .398 (±.076) μg/mg tissue. CHG, with and without 50% eucalyptus globulus leaf oil, was detected at negligible levels in receptor compartment over 24 h. This suggested that CHG did not permeate through full skin thickness, and was retained within tissue	[49]
Eucalyptus globulus leaf oil 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 mg/cm2/h) than the flux (20.1 mg/cm2/h) of a saturated solution of TMP without the oil	[50]
Eucalyptus globulus leaf oil (80% to 85% eucalyptol) 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 and applied to abdominal skin of sprague-Dawley rats in diffusion cells	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: Eucalyptus globulus leaf oil > transcutol > DMSO > *d*-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	[51]

(continued)

Table 13. (continued)

Ingredient/Substance	Drug	Details	Results	Reference
Eucalyptus globulus leaf oil 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). Receptor fluid was saline	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 > eucalyptus globulus leaf oil > peppermint oil > turpentine oil	[52]

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

enhancement ratios were 1.80, 3.04, and 3.68 for 5, 7.5, and 10%, respectively.[51] Eucalyptus Globulus Leaf Oil increased the dermal penetration of 5-fluorouracil (5-FU) through rat skin when using 2-chamber diffusion cells; the enhancement ratios ranged from 58.49 to 82.55, depending on temperature (100 - 140°C).[52]

Absorption, Distribution, Metabolism, and Excretion

Animal

Oral

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

Eucalyptol undergoes oxidation in vivo with the formation of hydroxycineole which is excreted as a glucuronide.[53,54] 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.

A gavage study on the metabolism of eucalyptol from rosemary oil (4, 20, or 40 µL rosemary oil containing 39% of eucalyptol (approximately equivalent to 52, 260, and 520 mg/kg eucalyptol, respectively) was conducted in NMRI mice (n = 5).[55,56] The rosemary oil was administered in an oil/water emulsion with 10% Tween 80 (.3 mL). Controls were administered water and Tween 80. Blood samples were collected at intervals over 90 min. There was rapid absorption and metabolism; blood concentrations of eucalyptol reached a peak 5 min. At the 52 mg/kg dose, the blood concentration of eucalyptol peaked at approximately 4.5 nL/g and then dropped to close to undetectable over 90 min. At 260 mg/kg, blood concentrations remained constant (between 7.0 and 10.1 nL/g) over the next 90 min, while at 520 mg/kg, the peak blood concentration peaked at 18.0 nL/g and then dropped to 60% of the maximum value after 10 min and remained in that range (9.1 to 12.2 nL/g) for the following 80 min. The slowing of the metabolism of eucalyptol at higher doses suggests saturation.

Inhalation

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

An inhalation study on the metabolism of eucalyptol from rosemary oil (.1, .3, .4, .5, or .6 mL rosemary oil containing 39% of eucalyptol; approximately equivalent to .039, .117, .156, .195, or .234 mL eucalyptol) was conducted in NMRI mice (n = 20 to 30).[56] The mice (5/cage) were placed into airtight cages in which rosemary oil was applied to filter paper and allowed to evaporate over an hour. The concentrations of rosemary oil and eucalyptol in the breathing air were 35 to 40 nL/mL and 13.7 to 15.6 nL/mL, respectively. Soda lime was used to remove the carbon dioxide, and calcium chloride was used to remove humidity. Oxygen was replaced through an opening in the cage. After an hour, the mice were killed and blood samples were collected. Immediately after exposure, eucalyptol blood concentration was approximately 4.5, 10, 10, 12, and 16 nL/g after doses of .039, .117, .156, .195, or .234 mL eucalyptol/cage, respectively. In a second experiment, mice (n = 5 to 10) were exposed to .195 mL eucalyptol. Blood samples were collected at intervals over 120 min. The eucalyptol blood concentration peaked at 16.2 nL/g and the elimination of the eucalyptol was biphasic. The concentration of eucalyptol dropped to approximately 5 nL/g in 30 min and approximately 1.5 nL/g at 120 min; there was a short half-life of 6 min during the first 10 min and a half-life of about 45 min during a second phase.

Toxicological Studies

Acute Dose Toxicity

Acute dermal and oral toxicity studies in animals that are summarized below are presented in Table 14.

Animal

Dermal. The dermal LD_{50} of Eucalyptus Globulus Leaf Oil was > 5000 mg/kg in rabbits.[10] There were no mortalities or signs of toxicity. The dermal LD_{50} of eucalyptol was > 5000 g/kg in rabbits.[54]

Table 14. Acute Dermal and Oral Toxicity.

Ingredient	Animal (n)	Concentration	Procedure	Results	Reference
Dermal					
Eucalyptus globulus leaf oil	Rabbits (10)	5000 mg/kg	Dermally administered to rabbits in a single dose. Rabbits were observed for 14 days	There were no mortalities or signs of toxicity. LD_{50} was > 5000 mg/kg	10
Eucalyptol (for inference to eucalyptus globulus leaf oil)	Rabbits	5000 mg/kg	Not provided	LD_{50} was > 5000 mg/kg	54
Oral					
Eucalyptus globulus leaf oil	Male ddY mice (n = 10)	2200, 2900, 3700, or 6200 mg/kg in olive oil	Administered by gavage and observed for 7 days. There was no control group	Mortalities were 10%, 20%, 70%, and 100% at 2200, 2900, 3700, or 6200 mg/kg, respectively. Surviving mice had reduced growth. LD_{50} was 3320 (confidence interval 2770 to 3980) mg/kg	10
Eucalyptus globulus leaf oil	Female albino swiss mice (n = 6)	An aqueous emulsion of 5% eucalyptus globulus leaf oil (with polysorbate-80 (2%) as an emulsifier; 0, .5, 1.0, 1.5, 2.0, 2.5, 3.0 3.5 mL/kg Control: The vehicle (2% polysorbate-80 and water)	Mice were fasted for 4 h prior to dosing and 2 h after dosing and observed every 30 min for 4 h, then daily for 14 days. Mice were then weighed, killed, and necropsied	There were no signs of toxicity or mortality in 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. Clinical signs disappeared in surviving mice, mostly after a day. In 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 appearance of observed internal organs (stomach, liver, and kidney) in all treatment groups. The LD_{50} of the emulsion was between 3 and 3.5 mL/kg	57

(continued)

Table 14. (continued)

Ingredient	Animal (n)	Concentration	Procedure	Results	Reference
Eucalyptus globulus leaf oil	SPF sprague-Dawley (SD) rats (n=5/sex)	0, 2772, 3267, 3960, 4752, and 5742 mg/kg in water with polysorbate-80 and span-80 as emulsifier	Administered by gavage	50 min after dosing in 5742 mg/kg group, rats appeared to move slowly, gather together, have extreme sensitivity to noise, and have convulsions. Rats in other treatment groups showed milder symptoms. 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 rats that died, large amounts of undigested feed and eucalyptus globulus leaf oil was observed in stomachs, and no tissue damage was observed except in lungs and liver (details of the damage was not provided). LD_{50} was 3811.5 mg/kg (confidence interval: 3326.4 and 4306.5 mg/kg)	[58]
Eucalyptus globulus leaf oil (method of manufacture is presented in Table 3)	Male albino Wistar rats (n=10)	500, 1000, 1,500, 2,000, or 2500 mg/kg	Administered by gavage. Mortality was determined after 24 h	The LD_{50} was 2334.3 mg/kg and the LD_{95} was 7632.13 mg/kg	[59]
Eucalyptus globulus leaf oil	Rats	Not specified	Administered by gavage	Rats that were near death could not feed themselves. LD_{50} was 4400 mg/kg	[10]
Eucalyptol	Mice	500 mg/kg	Administered by gavage	An increase in liver enzyme activity was also found in mice given 500 mg/kg orally	[53]
Eucalyptol	Rats	Not specified	Administered by gavage	LD_{50} = 2480 mg/kg	[53,54]
Eucalyptol	Rats	Not specified	Administered by gavage	LD_{50} = 1560 mg/kg Lethal dose caused rapid cyanosis and stupor accompanied by irregular breathing, extreme sensitivity to noise, convulsions, and death from respiratory failure	[53]

Oral. Eucalyptus Globulus Leaf Oil administered to mice (n = 10) by gavage had an oral LD_{50} of 3320 mg/kg.[10] The LD_{50} of an aqueous emulsion comprising 5% Eucalyptus Globulus Leaf Oil in mice was between 3 and 3.5 mL/kg.[57] 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. The oral LD_{50}s of Eucalyptus Globulus Leaf Oil were 3811.5 mg/kg,[58] 2334.3 mg/kg,[59] and 4400 mg/kg[10] in three different studies in rats. Mice orally administered a single dose of eucalyptol (500 mg/kg) had an increase in liver enzyme activity.[53] Reported oral LD_{50}s of eucalyptol in rats were 2480 mg/kg and 1560 mg/kg.[53,54]

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.[60] A second collecting tube was also installed. Water vapor 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 (.4 to 19 683 mg/kg body weight in ethyl alcohol; not known if leaf or leaf/twig oil) was added to the boiling water bath; respiratory tract fluid was collected from each rabbit 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 once each year in 2 successive years, and in each instance produced no significant change in any parameter measured. Local irritation of the respiratory tract appeared after administration of the two highest doses.

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

Ovalbumin (OVA)-sensitized guinea pigs were exposed to aerosolized eucalyptol for 15 min. The eucalyptol (1 mg/mL) was aerosolized using a nebulizer into a box ($21 \times 20 \times 30$ cm^3).[61] Approximately 3 min later, the guinea pigs were exposed to aerosolized saline for 15 min. The control group was exposed to aerosolized saline for both exposures. The guinea pigs were killed 24 h later and inflammatory parameters such as tracheal responsiveness to carbachol, cytokine levels and myeloperoxidase activity on bronchoalveolar lavage fluid, as well as mucociliary clearance were evaluated. There were no differences in the numbers of eosinophils, neutrophils, lymphocytes and macrophages in the treatment group compared to controls. Cytokine levels (IL-1, TNFα, and IL-10) were also similar between the two groups.

Human

Oral

Eucalyptus Globulus Leaf Oil

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

The probable oral lethal dose for adult humans is .05 to .5 mL/kg.[11] 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 wk. 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.

Oral ingestion of Eucalyptus Globulus Leaf Oil, as low as approximately 5 mL, can affect 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). 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; nephritis is rare but has been recorded. 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. 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.[11]

Inhalation

Eucalyptus Globulus Leaf Oil

The literature on the inhalation toxicity in humans of Eucalyptus Globulus Leaf Oil is scarce, and the following is a summary of this information. The substances are referred to in the literature 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.[11] Inhalation of vapor may be used medicinally and there are no data available on toxicity by this route. 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. Short-term oral toxicity studies summarized below are presented in Table 15.

Eucalyptus Globulus Leaf Extract

Aqueous Eucalyptus Globulus Leaf Extract (2000 mg/kg/d) orally administered (route not specified) to mice for

Table 15. Short-Term Oral Studies.

Ingredient (Dose)	Animal (n)	Procedure	Results	Reference
Eucalyptus globulus leaf extract (2000 mg/kg/day aqueous; .2 mL; method of manufacture is presented in Table 3)	Male swiss albino mice (10)	Orally administered for 10 days. Control group was administered distilled water. Extract was made fresh daily	There were no mortalities. Treated mice demonstrated general weakness and decrease in physical activity and had loss of body fur, ruffled fur, and changes in their white coat color. Treated mice had reduced feed intake and lost weight (−13.35%). There was a reduction in hemoglobin concentration (3.12%), PCV (3.11%), RBC (11.31%), and total WBC (20.97%), indicating severe leucopoenia. Platelet count was also reduced (15.55%). There were significant changes in enzymes demonstrating liver impairment: AST, 33.0 ± 1.0 vs 75.0 ± 1.0 IU/l, 127.27% increase and ALT 35.0 ± 1.0 vs 65.0 ± 1.0 IU/L, 85.71% increase. There was an increase in creatinine (1.90 ± .1 vs .09 ± .1 mg/dl) and urea levels (75.0 ± 1.0 vs 25.0 ± 1.0 mg/dl). Gross examination of treated mice showed pale livers, congestion and hemorrhages in lungs of some mice, enlarged spleens, and mild congestion in hearts in some mice. Histological examination of treated mice showed damage to hepatic cells manifested by swollen hepatocytes with vacuolated cytoplasm (very extensive in some cells). Many necrotic cells with pyknotic or karyolitic nuclei were observed. Some central veins of livers were congested and some hepatocytes had enlarged nuclei. Histological examination showed renal tubules of treated mice had mild to severe degeneration. Degenerative changes were in tubular epithelium reflecting failure of membrane ion pumps, allowing cells to accumulate fluid. Administration of eucalyptus globulus leaf extract caused significant neurodegenerative changes including a decrease in size and number of neurons in cerebral cortex. Many glial cells with dense fragmented nuclei were observed	[62]
Eucalyptus globulus leaf extract (0, 80, 100, or 120 mg/kg/day aqueous; 1 mL; method of manufacture is presented in Table 3)	Albino *Rattus norvegicus* rats (6)	Administered by gavage for 7 days. Controls were administered distilled water. Activities of ACP, ALP, SOD, and the level of MDA were determined in liver and serum	ACP and ALP activities were increased in livers with no difference in their serum activities. Activity of SOD was increased in livers in 100 and 120 mg/kg groups. There was an increase in level of MDA in livers of all treatment groups and in the serum of the 120 mg/kg group. Authors stated results indicate that aqueous eucalyptus globulus leaf extract may have deleterious effects on liver membrane structure and functional integrity	[63]
Eucalyptus globulus leaf extract (20 mL/day; method of manufacture is presented in Table 3)	Male Wistar rats (8)	Administered in drinking water (1 g/L) for 42 days. The rats consumed the equivalent of 130 mg dry leaves/day. A control group was administered water	There were no differences in creatinine, urea, protein, or uric acid in blood of both groups. In measurements of oxidative damage and antioxidant activities in kidneys, there were no differences in levels of peroxidation and activities, SOD, GPX, and CAT. There were no differences observed between the two groups when kidneys were examined microscopically	[64]
Eucalyptus globulus leaf oil (0, 1.5, or 2.0 mL/kg/day)	Female albino swiss mice (12/sex)	Administered by gavage for 84 days (12 weeks). Control group was administered the vehicle (2% polysorbate-80 and water). After last dose, blood samples were collected. Mice were killed and livers and kidneys examined	There were no signs of toxicity and no mortalities for either treatment group. Body weights were similar between treatment and control groups. There were no significant changes in hematological parameters in either treatment group compared to control group. General microscopic architecture of liver sections of mice in the 1.5 mL/kg group was similar to controls. Some areas of liver sections of mice in 2.0 mL/kg group showed that 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 1.5 mL/kg group showed no 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 2.0 mL/kg group	[57]

(continued)

Table 15. (continued)

Ingredient (Dose)	Animal (n)	Procedure	Results	Reference
Eucalyptus globulus leaf oil (0, 100, 300, or 1000 mg/kg/day; 4 mL/kg in corn oil)	Crl:CD(SD) rats (10/sex)	OECD GL 422 A combined repeated dose and reproduction/developmental study. Test substance was administered by gavage. Males were treated starting from 2 weeks before mating for at least 5 weeks. Females were treated from 2 weeks before mating until lactation day 6. Rats were killed and necropsied	One female in 1000 mg/kg/day group was found dead on day 15 after mating, which was not attributed to treatment. During first week of dosing, both males and females in 1000 mg/kg/day group displayed transient signs of reduced activity and unsteady muscle reactions. Rats in 1000 mg/kg/day group also displayed chin rubbing and salivation; salivation was also recorded in females in 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. Body weight gain of males in 1000 mg/kg/day group was low during week 1. During gestation, body weight gain and feed consumption was low in females in 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 level observed. Male rats at all doses had hyaline droplet nephropathy in 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_{2u}-globulin (produced by the liver) in the proximal tubules, which leads to subsequent damage and regeneration of tubular epithelium. 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. Absence of any tubular injury in test article treated females supports the conclusion that tubular degeneration is secondary to male specific hyaline droplet accumulation. All dose levels resulted in centrilobular hepatocytic hypertrophy in livers of males and an increase in glycogenic vacuolation in livers of females, which was considered an adaptive change likely associated with microsomal enzyme induction. A slight increase in incidence and severity of glycogenic vacuolation in livers of treated female compared with controls may be partially responsible for liver weight increase. Liver changes were not considered to be adverse. There were no microscopic correlates for decrease in spleen weight and increase in adrenal weight of high-dose females. 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 humans. NOAEL for females was 300 mg/kg based on effects on body weight and feed consumption	[10]
Eucalyptus globulus leaf oil (100, 300, or 1000 mg/kg/day in corn oil)	Crl:CD (SD) rats (3/sex)	Administered for 2 weeks	There were no mortalities. Clinical signs were salivation in isolated females in 300 and 1000 mg/kg/day groups, which authors considered minor and did not indicate an association with test material. Other signs were transient body weight loss and low feed consumption in males in 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 1000 mg/kg/day group. Thickening of mammary tissue was observed in 2 and 1 males in 300 and 1000 mg/kg/day groups, respectively, and 1 female in the 1000 mg/kg/day group. Under test conditions, LOAEL and NOAEL in female rats could be considered as 300 and 100 mg/kg/day, respectively, based on 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 male rats in this study. The LOAEL in male rats could be considered as 100 mg/kg bw/day	[10]

(continued)

Table 15. (continued)

Ingredient (Dose)	Animal (n)	Procedure	Results	Reference
Eucalyptus globulus leaf oil (0 or 233 mg/kg/dose in corn oil; 1/10 LD_{50}; method of manufacture is presented in Table 3)	Male albino Wistar rats (5/sex)	Administered by gavage every 3 days for 30 days. Blood samples were collected on days 15 (5^{th} dose) and 30 (10^{th} dose). Rats were then killed and necropsied	There was an 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. Activities of SGOT and SGPT enzymes were significantly increased at both 5th and 10th doses in treated rats. There were mild effects on kidney function in that there was an increase in creatinine and urea concentration at 10th dose. Histopathological studies on liver and kidney revealed relatively moderate pathological changes in liver as congestion of the blood vessels in portal area associated with inflammatory infiltration. There was also induced desquamation of epithelial cells of the renal tubules	59
Eucalyptus globulus leaf oil (0, 396, 792, and 1188 mg/kg in water with polysorbate-80 and span-80 as emulsifiers)	SPF sprague-Dawley (SD) rats (5/sex)	Administered by gavage for 30 days	There were no clinical signs during study period. In male rats, body weights of low-dose group was higher than control group; body weights of middle-dose group and high-dose group were lower than those of control group. In female rats, body weights of all of experimental groups were reduced. There were no differences in hematological parameters. Heart rates and respiratory rates were similar between groups. Serum biochemical parameters were similar between groups except that there were differences between control group and mid- and high-dose groups for: aspartate transaminase (increased), creatinine (increased), and glucose (decreased). There were no differences in organ weights. In livers of experimental groups, central venous extended with hyperemia and varying degrees of vacuolar degeneration of hepatocytes were observed. In spleens, red pulp extended with hyperemia and a large number of macrophages and langerhans cells infiltration was observed in 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 kidneys of mid- and high-dose groups. Histological examination showed that there were no differences with regard to heart, lung, stomach, intestines, testicles and ovaries	58
Eucalyptol (stomach tube: 150, 300, 600 and 1200 mg/kg/day Encapsulated form in diet: 3750, 7500, 15000 and 30000 mg/kg/day, equivalent to 600 to 5607 mg/kg/day for males and 705-6777 mg/kg/day for females.)	B6C3F1 mice (6/sex)	Administered 28 days either by stomach tube (5 days/week) or in encapsulated form with the diet	Liver weight/body weight ratio in males was increased at all but lowest dose given in encapsulated form as was brain weight/body weight ratio in females at the dose level. Microscopic examination revealed a minimal hypertrophy of centrilobular hepatocytes in mice of both sexes fed the encapsulated compound, especially at two highest dose levels	53
Eucalyptol (stomach tube: 150, 300, 600 and 1200 mg/kg/day Encapsulated form in diet: 3750, 7500, 15 000 and 30 000 mg/kg/day; 381 to 3342 mg/kg/day for males and 353 to 3516 mg/kg/day for females)	Fischer 344 rats (6/sex)	Administered for 28 days either by stomach tube (5 days/week) or in encapsulated form with the diet.	At dose levels of 600 mg/kg/day 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	53
Eucalyptol (0, 500, or 1000 mg/kg/day)	Male Wistar rats (10)	Administered by gavage for 28 days	There were decreases in terminal body weight and increased relative liver and kidney weights in both treatment groups. 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 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	53

ACP = acid phosphatase; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAT = catalase; GPX = glutathione peroxidase; IU = International units; LOAEL = lowest-observed-adverse-effect level; MDA = malondialdehyde; NOAEL = no-observed-adverse-effect level; OECD GL = Organisation of Economic Co-operation and Development Guidelines; PVC = packed cell volume; RBC = red blood cell count; SGOT = serum glutamic oxalacetic transaminase; SGPT = glutamic pyruvic transaminase; SOD = superoxide dismutase; WBC = white blood cell count.

Table 16. In Vitro Genotoxicity Studies.

Ingredient/ Substance	Assay	Details	Results	References
Eucalyptus globulus leaf extract	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	[10]
Eucalyptus globulus leaf oil	Bacterial reverse mutation assay	OECD GL 471; *S. typhimurium* (strains: TA98, TA100, TA1535, and TA1537) and *E. coli* (WP2) Experiment I (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	[10]
Eucalyptus globulus leaf oil	Human 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 .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	[10]

(continued)

Table 16. (continued)

Ingredient/ Substance	Assay	Details	Results	References
Eucalyptus globulus leaf oil	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	[10]
Eucalyptus globulus leaf oil	Somatic segregation assay	Using diploid strain of fungus *A. nidulans*, heterozygous for nutritional and conidia color markers. .12 and .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 *A. nidulans*. Genotoxicity of the oil was associated with induction of mitotic crossing-over or with oil-broken chromosomes	[12]
Eucalyptol	Ames assay	Concentration not specified *S. typhimurium* (TA98, TA100, TA1535, and TA1537)	No mutagenic effects with or without metabolic activation	[53]
Eucalyptol	Ames assay	Concentration not specified *S. typhimurium* (TA97a, TA98, TA100, and TA102)	No mutagenic effects with or without metabolic activation	[53]
Eucalyptol	Chromosome aberration assay	Concentration not specified CHO cells	No induced chromosome aberrations with or without metabolic activation	[53]
Eucalyptol	Sister chromatid exchange assay	Concentration not specified CHO cells	Sister chromatid exchanges were induced in CHO cells only in the absence of metabolic activation at doses that induced cell cycle delay	[53]
Eucalyptol	Rec assay	Concentration not specified *B. subtilis*	No evidence of DNA damage	[53]
Eucalyptol	Rec assay	Concentration not specified *B. subtilis*	No evidence of DNA damage	[53]

CHO = Chinese hamster ovary; MSO = Dimethyl sulfoxide; OECD GL = Organisation for Economic Co-operation and Development Guideline.

10 d caused no mortalities, but did cause general weakness and decrease in physical activity.[62] There were significant neurodegenerative changes, including a decrease in size and number of neurons in the cerebral cortex.

Aqueous Eucalyptus Globulus Leaf Extract (0, 80, 100, or 120 mg/kg) administered by gavage to rats for 7 d caused a significant increase in the level of malondialdehyde (MDA) in the liver of all treatment groups and in the serum of the 120 mg/kg group.[63] In a 42-d drinking water study in rats of an aqueous/ethanol Eucalyptus Globulus Leaf Extract (1 g/L), the rats consumed the equivalent of 130 mg dry leaves/d. Consuming the extract caused no changes in creatinine, urea, protein, or uric acid in the blood.[64]

Eucalyptus Globulus Leaf Oil. Eucalyptus Globulus Leaf Oil (0, 1.5, or 2.0 mL/kg/d), administered by gavage to mice for 12 wk, caused no signs of toxicity and no mortalities for either treatment group; however, kidney effects (pyknosis

Table 17. Dermal Irritation and Sensitization.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Irritation					
Alternative studies					
Eucalyptol (for inference to eucalyptus globulus leaf oil)	Neat	Human epidermis model	EpiSkin	Relative mean viability of treated tissue was 88.9% after 15 min exposure. Eucalyptol was predicted to be a non-irritant	[66]
Animal					
Eucalyptus globulus leaf oil	Neat	Hairless mice (n not specified)	Dermally administered to backs	Not irritating	[67]
Eucalyptus globulus leaf oil	Neat; 5000 mg/kg	Rabbits (n =10)	Single dermal dose. Observed for 14 days	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	[10]
Eucalyptus globulus leaf oil	Neat	Rabbits (n not specified)	Administered to abraded and intact skin under occlusion for 24 h	Moderately irritating	[67]
Eucalyptol (for inference to eucalyptus globulus leaf oil)	Range not specified	Albino mice (n = 10)	Open mouse ear assay	ID_{50} was 1.008 g/5 L acetone (.0202%)	[10]
Eucalyptol (for inference to eucalyptus globulus leaf oil)	100%	Rabbits (n not specified)	Administered to abraded and intact skin under occlusion for 24 h	Not irritating	[54]
Human					
Eucalyptus globulus leaf oil	10% in petrolatum	48h, n = 25; 24 h, n = 20	Administered under occlusion for 24 or 48 h	Not irritating	[67]
Eucalyptol (for inference to eucalyptus globulus leaf oil)	16% in petrolatum	n = 25	Administered under occlusion for 48 h	Not irritating	[54]
Sensitization					
Animal					
Eucalyptol (for inference to eucalyptus globulus leaf oil)	25% and 50% v/v in acetone/olive oil 4:1, and 100% v/v	Female mice (n = 5)	Local lymph node assay	SIs were: 25%, 1.43; 50%, 2.03; 100%, 5.08. 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 at 100%, but not at 25% and 50%, under the conditions of the test	[66]
Eucalyptol (for inference to eucalyptus globulus leaf oil)	.25%; .1 mL	Harley albino guinea pigs (n = 10)	Modified Draize test. Administered by intradermal injection to the clipped flanks at 4 sites which overlie the two auxiliary inguinal lymph nodes. After a 14-day non-treatment period, an intradermal injection of eucalyptol (.25%; .1 mL) was administered in one flank and a topical challenge (50%; .1 mL) was administered to the other flank and not covered. Test sites were scored 24 h after challenge, and scored and challenged again 7 days after first challenge. If there were no signs of irritation or sensitization, the procedure was repeated	Eucalyptol was found to be a non-sensitizer	[68]

(continued)

Table 17. (continued)

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Human					
Skin cream that contained eucalyptus globulus leaf oil	.1%	n = 52	HRIPT Open and occlusive patches were administered 3 days per week for 10 applications. For occlusive patches, test substance was applied to pad of a bandage strip and put onto skin of upper back. Open patches were applied to volar surface of left arm. Both series of patches were read 48 h after administration. After ~ 2 weeks after last inductions, patches were repeated and read 48 h after administration	Occlusive patch sites - 6 subjects had a weak, non-vesicular reaction (+) at 1 to 6 of the induction readings. None of the subject had a reaction after the challenge patch	[69]
Lipstick that contained eucalyptus globulus leaf oil	.5%; 20 mg	n = 107	HRIPT A total of 9 induction patches (48 or 72 h), using Finn chambers, were administered to one side of the back in infrascapular area. Test sites were examined for erythema, edema and other signs of cutaneous irritation before the next application. After a 2-week rest, challenge application was administered on opposite side of the back, which remained in place for 24 h. Challenge site was examined at 30 min and 48 h after removal	There were no adverse events reported. It was concluded that there was no evidence of irritation or sensitization for this test substance	[70]
Eucalyptus globulus leaf oil	10% in petrolatum	n = 25	Maximization assay	Not sensitizing. No further details were provided	[67]
Skin cream that contained eucalyptus globulus leaf oil	.1%	n = 101	Schwartz-Peck prophetic patch test Conducted using open and occlusive patches. For occlusive patch, test substance was applied to pad of a bandage strip and put onto cleaned skin of upper back. Open patch was applied to volar surface of left arm. Both patches were read 48 h after administration. After ~ 2 weeks, patches were repeated and read 48 h after administration	In closed patches, a weak, non-vesicular reaction (+) was observed in 4 subjects at first challenge reading, but not second, and in 2 other subjects only at second reading. In the open patches, there were no reactions observed at either reading	[69]
Eucalyptol (for inference to eucalyptus globulus leaf oil)	16% in petrolatum	n = 25	Maximization assay	No signs of sensitization	[54]

HRIPT = human repeated insult patch test; ID_{50} = irritation dose in 50% of test individuals; SI = stimulation index.

Table 18. 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 (.6%) had positive results; 2 of these subjects had reactions with macular erythema and 2 had weak reactions	[92]
2% in petrolatum	96	Patch tests of subjects in a practice that specializes in contact dermatitis and eczema. Location of facility not provided	5 subjects had positive reactions; 2 of the scored with a +/− reaction, 2 with a + reaction, and 1 with a ++ reaction	[75]
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)	.24% of those tested had positive reactions; .41% scored with a ?/irritant reaction, .19% with a + reaction, and .06 with a ++/+++ reaction	[72]
Not specified (in finished cosmetic products containing unspecified concentrations of eucalyptus globulus leaf oil)	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 with 1 of 23 bath and shower products and 1 of 88 skin care products; reactions were not observed for products containing "eucalyptus oil" in the other 13 cosmetic product categories	[73]
Not specified	200	Patch tests of subjects with dermatitis at the Warsaw Medical school, Poland	3 subjects had positive reactions	[76]
Not specified	450	Patch tests of subjects with dermatitis at the Warsaw Medical school, Poland	5 subjects had positive reactions	[77]
Not specified	5315	Patch tests of subjects with dermatitis at the st. John's Hospital for diseases of the skin in london	1 subject had a positive reaction	[74]

of renal tubular epithelial cells and widening of tubular lumen) and liver effects (pyknosis, vacuolations of hepatocytes, and focal necrosis) were observed in the high-dose group at necropsy.[57]

In a combined repeated dose and reproductive/developmental study, Eucalyptus Globulus Leaf Oil (0, 100, 300, or 1000 mg/kg/d) orally administered by gavage to rats caused transient signs of reduced activity and unsteady muscle reactions, multiple changes in blood chemistry, hyaline droplet nephropathy in the kidneys of male rats, and centrilobular hepatocytic hypertrophy in the livers of male rats and an increase in glycogenic vacuolation in the livers of female rats.[10] Males were treated starting from 2 wk before mating for at least 5 wk; females were treated from 2 wk before mating until lactation day 6. The no-observed-adverse-effect level (NOAEL) for males was 1000 mg/kg/d based on hyaline droplet nephropathy at all dose levels; however this response is considered to be rat specific and to have no counterpart in humans. The NOAEL for females was 300 mg/kg/d based on effects on body weight and feed consumption.

Eucalyptus Globulus Leaf Oil (100, 300, or 1000 mg/kg/d) orally administered by gavage to rats for 2 wk caused no mortalities.[10] The lowest-observed-adverse-effect level (LOAEL) and NOAEL in female rats could be considered as 300 and 100 mg/kg/d, respectively, based on the clinical signs at 300 and 1000 mg/kg/d and increased liver weight at 1000 mg/kg/d. 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/d.

Table 19. Case Reports of *Eucalyptus globulus* Exposure.

Summary	Reference
Dermal	
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 a 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	[80]
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	[82]
Eucalyptus globulus leaf oil was used to treat a 42-year-old man with an infection after a mid-foot fracture and dislocation. The infected tissue was surgically debrided and a cream containing eucalyptus globulus leaf oil (.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	[82]
A 12-year-old boy splashed eucalyptus globulus leaf oil (amount unknown) on his face. No symptoms developed	[83]
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	[83]
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% eucalyptol 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	[79]
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%	[81]
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 at days 2 and 4; the other ingredients of the cream were negative. The controls were all negative at days 2 and 4	[84]
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 well by next morning	[11]
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	[11]
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, foaming at 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	[11]
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	[11]

(continued)

Table 19. (continued)

Summary	Reference
A 7 month old boy was offered a teaspoonful of 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 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	85
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	86
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 within an hour of his death	11
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. 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	88
A 6-year-old child was administered approximately 15 mL of eucalyptus globulus leaf oil and experienced only slight drowsiness	11
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	83
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	83
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	87
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	87
Inhalation	
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 *Eucalyptus* 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 *Eucalyptus* 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 *Eucalyptus* sp. performed 1 month apart. All stimuli were applied to gauze held approximately 5″ from the nares. Dry *Eucalyptus* sp. leaves were used to impregnate the test gauze. The initial challenge was with *Eucalyptus* 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-*Eucalyptus* 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	89
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 to 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 (.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	90

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

Eucalyptus Globulus Leaf Oil (0 or 233 mg/kg/dose in corn oil) administered by gavage every 3 d for 30 d caused an increase in white blood cell (WBC) counts and a decrease in hemoglobin concentration and platelets count in both blood samples, and relatively moderate pathological changes in the liver as congestion of the blood vessels in the portal area associated with inflammatory infiltration.[59]

Eucalyptus Globulus Leaf Oil (0, 396, 792, and 1188 mg/kg/d) administered by gavage for 30 d caused no clinical signs, but changes to aspartate transaminase (increased), creatinine (increased), and glucose (decreased) in serum chemistry in the mid- and high-dose groups were observed.[58] In the livers of the experimental groups, the central veins were distended with hyperemia and varying degrees of vacuolar degeneration of hepatocytes were observed.

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

Eucalyptol (150, 300, 600, and 1200 mg/kg/d) administered by stomach tube or in encapsulated form in feed (600 to 5607 mg/kg/d for males and 705 to 6777 mg/kg/d for females) to mice for 28 d caused increased relative liver weights in all but the lowest dose in feed and a minimal hypertrophy of centrilobular hepatocytes in both sexes, especially in the two highest dose levels.[53]

Eucalyptol (150, 300, 600, and 1200 mg/kg) administered by stomach tube or in encapsulated form in feed (381 to 3342 mg/kg/d for males and 353 to 3516 mg/kg/d for females) to rats for 28 d caused a dose-dependent decrease of body weight gain starting at 600 mg/kg and an absence of a normal degree of hepatic centrilobular cytoplasmic vacuolization was observed in male rats.[53] Eucalyptol (0, 500, or 1000 mg/kg/d) orally administered by gavage to male rats for 28 d caused no changes in the brain, but minor focal infiltration of mononuclear cells in liver was observed in both treatment groups and a dose-related accumulation of eosinophilic protein droplets containing α_{2u}-globulin in the cytoplasm of proximal tubular epithelial cells was observed in kidneys.[53]

Subchronic Toxicity Studies

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

Chronic Toxicity Studies

Oral

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil). A toothpaste containing eucalyptol (0, 8, and 32 mg eucalyptol/kg/d; 1 mL toothpaste) was administered by gavage to pathogen-free CFLP mice (n = 52) 6 d/wk for 80 wk, followed by 16 and 24 wk of rest.[53] 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.

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/kg/d; in corn oil) was administered by gavage to Crl:CD(SD) rats (n = 10/sex).[10] The study was conducted in accordance with Organisation of Economic Co-operation and Development Test Guideline (OECD TG) 422. Males were treated starting from 2 wk before mating for at least 5 wk; females were treated from 2 wk before mating until lactation day 6. The adults and offspring rats were then killed and necropsied. [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 of the treatment groups at birth were similar to that of the control group. However, body weight gains of male and female offspring in the 1000 mg/kg/d 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. A slightly increased incidence of "cold to touch" was observed in litters in the 1000 mg/kg/d group. At microscopic examination, there were no findings attributed to treatment for offspring that died and were examined during the experiment or were killed and examined at the end of the experiment.

Under the test condition, the NOAEL for the females was considered to be 300 mg/kg/d 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 body weight 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/d, which was based on lower offspring body weight gain, and clinical signs (pups cold to touch) that were only observed in the 1000 mg/kg/d 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/d, since no adverse effects were observed for any reproductive parameters.

Genotoxicity Studies

In Vitro

Genotoxicity studies are summarized in Table 16.

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.[10] 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.[10] 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.[10] Eucalyptus Globulus Leaf Oil at .12 and .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.

Eucalyptol (concentration not specified) was not mutagenic in Ames assays, with and without metabolic activation. Eucalyptol (concentrations not specified) was not mutagenic to Chinese hamster ovary (CHO) cells in a chromosome aberration assay and a sister chromatid exchange assay, with and without metabolic activation. Eucalyptol (concentration not specified) was not mutagenic in rec assays using *Bacillus subtilis*.[53]

Carcinogenicity Studies

No published carcinogenicity studies were discovered and no unpublished data were submitted on the *Eucalyptus globulus* (eucalyptus)-derived ingredients in this safety assessment.

Eucalyptol (for Inference to Eucalyptus Globulus Leaf Oil)

A toothpaste containing eucalyptol (0, 8, or 32 mg/kg/d) was administered by gavage to male pathogen-free CFLP mice (n = 52) for 80 wk.[65] The controls were administered nothing (n = 52) or the toothpaste base (n = 260). The mice were observed daily, and were weighed weekly for the first 6 wk of the study then every 2 wk. Mice found dead were necropsied. At week 80, the mice were killed and organ weights for the kidneys, adrenals, lungs, liver, and spleen were examined. All macroscopically identified tumors were examined histopathologically. Tissues from the kidneys, liver, lungs, and brain were also examined histopathologically. All of the mice in the low-dose group and 47 of the mice in the high-dose group were necropsied. There were no differences between the test groups and the control and vehicle control groups in the incidence or severity of tumors of the organs or the presence of malignant lymphoma.

Tumor Promotion

Dermal

Eucalyptus Globulus Leaf Oil. Eucalyptus Globulus Leaf Oil was tested for tumor promotion in mice.[29] A single application of 9,10-dimethyl-1,2-benzanthracene (DMBA) was administered to the clipped backs of 8-wk-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 (.25 mL/wk) was administered to the backs of the mice once per week for 33 wk. 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 and sensitization studies are summarized in Table 17.

Irritation

Eucalyptol (100%) was predicted to be a dermal non-irritant in an EpiSkin™ assay.[66] Eucalyptus Globulus Leaf Oil (neat) was not dermally irritating to hairless mice,[67] but was slightly (neat; 5000 mg/kg) or moderately (intact and abraded skin) irritating to rabbits.[10,67] In an open mouse ear assay of eucalyptol using albino mice (n = 10), the irritant dose in 50% of test individuals (ID_{50}) was 1.008 g/5 L acetone (.0202%).[10] Eucalyptol (100%) administered to intact and abraded skin of rabbits for 24 h under occlusion was not irritating.[54] Eucalyptus Globulus Leaf Oil (10% in petrolatum)[67] and eucalyptol (16% in petrolatum) were not irritating to human subjects (n = 25).[54]

Sensitization

Eucalyptol (25% and 50% v/v) tested in a local lymph node assay (LLNA) using female mice (n = 5) was considered to be a sensitizer at 100%, but not at 25% and 50%.[66] In a Draize test using Harley albino guinea pigs (n = 10),

eucalyptol (.25%; .1 mL) was not irritating or sensitizing.[68]

In multiple human repeated insult patch tests (HRIPT), cosmetic formulations containing Eucalyptus Globulus Leaf Oil (up to .5%) were found to be non-irritating.69,70 In a maximization assay in human subjects (n = 25), Eucalyptus Globulus Leaf Oil (10% in petrolatum) produced no sensitization reactions.[67]

Photosensitization/Phototoxicity

In Vitro

Eucalyptus Globulus Leaf Oil. An in vitro photohemolysis test (human erythrocyte suspensions) was used to evaluate the phototoxicity of Eucalyptus Globulus Leaf Oil (.001, .01, or .1% in alcohol).[71] The ultraviolet A (UVA; long-wave)-rich light source was a UVASUN 5000 lamp (320 to 460 nm; 42 mW/cm^2) and the ultraviolet B (UVB; mid-wavelength)-rich light source was a lamp with TL 20 W/12 light bulbs (between 275 and 365 nm; 1 mW/cm^2 (UVB) and .4 mW/cm^2 (UVA)). There was no hemolysis observed under the test conditions. The authors concluded that the test substance is not expected to be photosensitizing.

Human

In a Draize-Shelanski HRIPT, a skin cream that contained Eucalyptus Globulus Leaf Oil (.1%; no dose specified), was tested on the backs of 52 subjects and exposed to UV light at a distance of 12" (30.48 cm) for 1 min. These exposures were after the first, fourth, seventh, and 10th induction patches and the challenge patch were read.[69] The test sites were read 48 h after each application. Induction applications were rotated between three sites on the back of each subject; therefore, irradiation was administered to the same test site every third patch. The challenge was administered to a naïve site. There were no signs of photosensitization in any subject at any reading. [See Sensitization section for sensitization data.]

In a Schwartz-Peck prophetic patch test, photosensitization potential of a skin cream containing Eucalyptus Globulus Leaf Oil (.1%) (n = 101) was evaluated at the occlusive patch sites.[69] The test sites were exposed to an UV light (at a distance of 12" (30.48 cm) for 1 min) 48 h after the second patch was administered. The test sites were read 48 h after the UV exposure. There were no signs of photosensitization in any subject. [See Sensitization section for sensitization data.]

Ocular Irritation Studies

In Vitro

Eucalyptol (for Inference to Eucalyptus Globulus Leaf Oil). Eucalyptol (100%; .75 mL) was tested in a bovine corneal opacity and permeability assay.[66] Eucalyptol was not considered to be an ocular corrosive or severe irritant.

Animal

Eucalyptus Globulus Leaf Oil. In an eye irritation study performed in accordance with OECD TG 405 (acute eye irritation/corrosion), undiluted Eucalyptus Globulus Leaf Oil (.1 mL) was instilled into the right eye of a single New Zealand White (Hsdlf:NZW) rabbit.[10] 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 for cornea opacity, .0/0.0/0.0 for iris lesions, .7/1.0/0.7 for redness of the conjunctivae, and .7/0.7/0.7 for chemosis. One rabbit had no body weight gain and two rabbits showed expected gain in body weight during the study.

Clinical Studies

Retrospective and Multicenter Studies

Dermal. Dermal retrospective and multicenter studies of Eucalyptus Globulus Leaf Oil are summarized in Table 18. 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 (.6%) had positive results in sensitization studies with Eucalyptus Globulus Leaf Oil (2%). 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, .24% had positive reactions.[72] 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.[73]

In sensitization tests (method not reported) of patients (n = 5315) in London with dermatitis, 1 subject had a positive reaction to Eucalyptus Globulus Leaf Oil (concentration not specified).[74] In patch tests of subjects (n = 96) with dermatitis and/or eczema, 5 subjects had positive

reactions (2 scored with a +/− reaction, 2 with a + reaction, and 1 with a ++ reaction) to Eucalyptus Globulus Leaf Oil (2% in petrolatum).[75]

In sensitization tests (method not clear) of patients (n = 200) in Poland with dermatitis, 3 subjects had positive reactions to Eucalyptus Globulus Leaf Oil (concentration not specified).[76] When this study was continued on additional patients (n = 450) with dermatitis, 5 subjects had a positive reaction to Eucalyptus Globulus Leaf Oil (concentration not specified).[77]

Oral. In a respective study of accidental ingestion of Eucalyptus Globulus Leaf Oil by children in Australia (n = 109), 41% had no effects, 30% resulted in minor poisoning, 25% resulted in moderate poisoning, and 3% resulted in severe and life threatening poisoning.[78] Of those where the volume was known, 17 ingested 100% oil and 10 ingested inhalation preparations. All of those children who had been given Eucalyptus Globulus Leaf Oil by a parent or guardian by mistake ingested a mean volume of 2.2 mL (range, .2 - 7.5 mL). There were no deaths. Adverse effects included vomiting, depression of conscious state, ataxia, pulmonary disease, miosis, and abdominal pain.

Case Reports

Case reports of adverse reactions to dermal, oral, and inhalation exposure to Eucalyptus Globulus Leaf Oil are presented in Table 19.

Dermal effects ranged from none to eczema, erythematous macular lesions, papules and vesicles, and/or pruritus.[79-84] Oral effects included esophageal pain, gasping for breath, restlessness, dyspnea, weak pulse, vomiting, drowsiness, and convulsions.[11,83,85-88] Inhalation effects included strong characteristic smell on the breath, coughing, chest tightness, dyspnea, hoarseness, and wheezing.[83,89]

In children, inhalation 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.[90]

Summary

This is a review of the safety of 6 *Eucalyptus globulus*-derived ingredients as used in cosmetics. According to the *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.

Because Eucalyptus Globulus Leaf Oil consists of not less than 70% (w/w) eucalyptol, relevant toxicity data on eucalyptol are included as supporting information in this safety assessment. Other reported main components of Eucalyptus Globulus Leaf Oil include α-pinene (9.22 - 24.6%), globulol (.819 - 2.817%), and β-pinene (.217 - 1.237%), depending on the origin of the plant.

According to VCRP survey data received in 2018, Eucalyptus Globulus Leaf Oil is reported to be used in 433 formulations (214 leave-on formulations, 160 rinse-off formulations, and 59 formulations that are diluted for the bath). Eucalyptus Globulus Leaf Extract is reported to be used in 77 formulations and Eucalyptus Globulus Leaf Powder is reported to be used in 2 formulations. The VCRP included ingredients with the non-INCI name "eucalyptus" (42 reported uses) and "eucalyptus extract" (11 reported uses). The results of the concentration of use survey conducted by the Council in 2017 and 2018 indicate Eucalyptus Globulus Leaf Water is used at up to 1.4% in face and neck products. The rest of the ingredients with reported concentrations of use are used at 1.2% or less. There were no uses reported to the VCRP or industry survey for Eucalyptus Globulus Leaf/Twig Oil.

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

Orally administered eucalyptol undergoes oxidation in vivo with the formation of hydroxycineole which is excreted as a glucuronide. In rats, urinary metabolites were 2-hydroxycineole, 3-hydroxycineole, and 1,8-dihydroxycineol-9-oic acid. In mice, eucalyptol is rapidly absorbed and metabolized; when inhaled, elimination was biphasic.

The dermal LD_{50} for Eucalyptus Globulus Leaf Oil and eucalyptol was > 5000 mg/kg in rabbits. The oral LD_{50} for Eucalyptus Globulus Leaf Oil was 3320 mg/kg in male mice. At doses at and above 2.5 mL/kg, toxic effects were observed; the clinical signs disappeared in surviving mice. In rats, the oral LD_{50} for Eucalyptus Globulus Leaf Oil was reported as 3811.5 mg/kg in one study and 4400 mg/kg in another study. Reported oral LD_{50}s of eucalyptol in rats were 2480 mg/kg and 1560 mg/kg.

Rabbits inhaling water vapor containing Eucalyptus Globulus Leaf Oil died; the output of respiratory tract fluid was significantly augmented at 19 683 mg/kg. OVA-sensitized guinea pigs exposed to aerosolized eucalyptol for 15 min showed no pulmonary effects.

The probable oral lethal dose of Eucalyptus Globulus Leaf Oil for adult humans is .05 mL to .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. In humans, inhalation of Eucalyptus Globulus Leaf Oil, either as liquid or aerosol, may result in pneumonitis.

An aqueous Eucalyptus Globulus Leaf Extract (2000 mg/kg/d) orally administered to mice for 10 d caused no adverse effects. In short-term oral toxicity studies, Eucalyptus Globulus Leaf Extract administered to rats showed hepatic effects in some studies (starting at 100 mg/kg) and none in another (1 g/L in drinking water for 42 d).

In short-term oral toxicity studies, Eucalyptus Globulus Leaf Oil and eucalyptol caused hepatic effects in both mice and rats. Oral administration of Eucalyptus Globulus Leaf Oil for 12 wk caused renal and hepatic effects at 2.0 mL/kg/d in mice, but not at 1.5 mL/kg/d. In rats, hepatic effects were observed starting at 233 mg/kg Eucalyptus Globulus Leaf Oil. Eucalyptol (150 to 1200 mg/kg/d) administered by stomach tube or in feed (600 to 5607 mg/kg/d for males and 705 to 6777 mg/kg/d for females) to mice for 28 d caused increased relative liver weights in all but the lowest dose in feed. Eucalyptol (500 or 1000 mg/kg/d) orally administered for 28 d to rats caused minor focal infiltration of mononuclear cells in livers in both treatment groups. There were no treatment-related effects in mice orally administered a toothpaste containing up to 32 mg eucalyptol/kg/d for 80 wk.

In a reproduction/developmental study of Eucalyptus Globulus Leaf Extract administered to rats, the NOAEL for the females was 300 mg/kg/d for systemic toxicity, based on lower body weight gain and feed consumption during gestation. The NOAEL for developmental toxicity was 300 mg/kg/d, which was based on lower offspring body weight gain, and clinical signs that were only observed in the 1000 mg/kg/d group. However, a NOAEL at 300 mg/kg/d was determined for systemic effect in the offspring based on the magnitude of the weight reduction. The NOAEL for reproductive toxicity was 1000 mg/kg/d, 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. Eucalyptus Globulus Leaf Oil was not genotoxic in a bacterial reverse mutation assay (up to 5000 µg/plate), in an in vitro mammalian chromosome aberration test (up to1000 µg/ml) and an in vitro mammalian cell gene mutation test using mouse lymphoma L5178Y cells (up to 300 µg/mL). However, Eucalyptus Globulus Leaf Oil at .12 µL/mL was found to increase the mitotic instability of the original diploid strain and the number of diploid mitotic recombinants of *A. nidulans*. Eucalyptol was not mutagenic in Ames assays, to CHO cells in a chromosome aberration assay, a sister chromatid exchange assay, and in rec assays using *B. subtilis*.

There were no differences between the test groups and the untreated control and vehicle control groups in the incidence or severity of tumors of the organs or the presence of malignant lymphoma in male mice administered a toothpaste containing eucalyptol (0, 8, or 32 mg/kg/d) for 80 d. In mice first treated with a single dermal dose of DMBA then dermally administered .25 mL Eucalyptus Globulus Leaf Oil (neat) weekly for 33 wk, papillomas were observed in 4 of 14 mice. None of the 13 control mice had papillomas.

Eucalyptol (100%) was predicted to be a non-irritant in an EpiSkin™ assay. Eucalyptus Globulus Leaf Oil (neat) was not dermally irritating to hairless mice, but was slightly (neat; 5000 mg/kg) or moderately (intact and abraded skin) irritating to rabbits. In an open mouse ear assay of eucalyptol using albino mice (n = 10), the ID_{50} was 1.008 g/5 L acetone (.0202%). Eucalyptol (100%) administered to intact and abraded skin of rabbits for 24 h under occlusion was not irritating. Eucalyptus Globulus Leaf Oil (10% in petrolatum) and eucalyptol (16% in petrolatum) were not irritating to human subjects.

Eucalyptol tested in an LLNA using female mice (n = 5) had an EC3 of 65.90%, thus was predicted to be a sensitizer at 100%, but not at 50%. In a Draize test using Harley albino guinea pigs (n = 10), eucalyptol (.25%; .1 mL) was not irritating or sensitizing. No dermal irritation or sensitization was reported in HRIPTs of cosmetic formulations containing Eucalyptus Globulus Leaf Oil up to .5%. In a maximization assay in human subjects (n = 25), Eucalyptus Globulus Leaf Oil (10% in petrolatum) produced no sensitization reactions.

In an in vitro photohemolysis test, Eucalyptus Globulus Leaf Oil (neat) was not predicted to be photosensitizing. In combined sensitization and photosensitization tests, there were no signs of photosensitization in two photosensitization patch tests of a skin cream that contained Eucalyptus Globulus Leaf Oil (.1%).

Eucalyptol (100%) was not considered to be an ocular corrosive or severe irritant when tested in a bovine corneal opacity and permeability assay. In rabbits, Eucalyptus Globulus Leaf Oil (1 mL) caused moderate conjunctival irritation in all treated eyes 1 h after treatment. Conjunctival irritation was minimal at 24- and 48-h 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 (.6%) had positive results for Eucalyptus Globulus Leaf Oil (2%). 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, .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 patients (n = 5315) in London with dermatitis, 1 subject had a positive reaction to Eucalyptus Globulus Leaf Oil (concentration not specified).

In a respective study of accidental ingestion of Eucalyptus Globulus Leaf Oil by children, adverse effects included vomiting, depression of conscious state, ataxia, pulmonary disease, miosis, and abdominal pain. 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, dyspnea, weak pulse, vomiting, drowsiness, and convulsions. Inhalation effects included coughing, chest tightness, dyspnea, hoarseness, and wheezing. In children, inhalation 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

The Panel examined the data on oral, dermal and inhalation toxicity, ocular and dermal irritation, sensitization, reproduction, genotoxicity, and phototoxicity. The Panel also considered toxicity data on eucalyptol, a major component of Eucalyptus Globulus Leaf Oil and Eucalyptus Globulus Leaf/Twig Oil. The Panel noted the lack of toxicity and the lack of irritation and sensitization at relevant concentrations of these ingredients. The genotoxicity studies and the carcinogenicity study on eucalyptol were negative and gave no cause for concern.

Case studies described adverse effects following both oral and dermal administration. Instances were reported in which persons who consumed *Eucalyptus globulus* oil became very ill following oral ingestion, with respiratory difficulties (e.g., pneumonitis, pulmonary edema, and bronchopneumonia) reported. The Panel noted that these incidents resulted from bolus doses and exposure was much greater than that expected with cosmetic use. Also, the Panel believes that the cause of the respiratory difficulties was aspiration of vomitus and not directly caused by *Eucalyptus globulus* oil. The adverse effects in the dermal case studies resulted from administration of *Eucalyptus globulus* oil at far greater concentrations than that found in cosmetics. Oral ingestion, and the circumstances of the dermal administration of *Eucalyptus globulus* oil, would lead to a rapidly increased concentration of the oil in the blood that would far exceed what would result from the use of cosmetic formulations containing Eucalyptus Globulus Leaf Oil. These high concentrations in the blood could not be obtained through cosmetic use.

The composition data are robust for Eucalyptus Globulus Leaf Extract and Eucalyptus Globulus Leaf Oil. The data on these two ingredients provide substantial insight into the other ingredients for which composition data are not as robust, and enable consideration of the entire group.

The sensitization data on Eucalyptus Globulus Leaf Oil at 10% and eucalyptol at 16% in humans provided evidence that sensitization at reported concentrations (maximum of 1.4%) of use should not be expected. This is supported by a LLNA and a Draize test in guinea pigs.

There is the possibility of the presence of potential sensitizers in the *Eucalyptus globulus*-derived ingredients because these constituents exist in the plant. However, if these constituents were to be present in a cosmetic formulation, the concentrations would be far below the level of toxicological concern. The impurity specifications of trade name mixtures containing Eucalyptus Globulus Leaf Extract, the lack of dermal irritation in human patch testing, the lack of sensitization in HRIPTs, and the small proportion of positive results in retrospective studies involving relatively large numbers of individuals assured the Panel that dermal irritation and sensitization from these constituents is not a significant concern in the cosmetic use of *Eucalyptus globulus*-derived ingredients. Relevant data on eucalyptol also contributed to support for this supposition. However, because final product formulations may contain multiple botanicals, each possibly containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. For *Eucalyptus globulus*-derived ingredients, the Panel was concerned about the presence of geraniol, limonene, and linalool in cosmetics, which could result in sensitization. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects. The Panel noted that IFRA standards have been developed, and published, so as to prevent adverse effects for several such constituents (Table 10).

The Panel expressed concern about pesticide residues, heavy metals, and substances from plants of other species (weeds) that may be present in botanical ingredients. To address these concerns, the cosmetics industry should continue to use current good manufacturing practices (cGMP) to limit impurities.

The Panel recognized that Eucalyptus Globulus Leaf Oil can enhance the penetration of other ingredients through the skin (e.g., chlorhexidine). The Panel cautioned that care should be taken in formulating cosmetic products that may contain this ingredient in combination with any ingredients whose safety was based on their lack of dermal absorption data, or when dermal absorption was a concern.

The Panel discussed the issue of incidental inhalation exposure from formulations that may be aerosolized (e.g., colognes and toilet waters at up to .4%). The acute inhalation data and historic case studies available suggest potential respiratory effects only at doses much greater than would be used in cosmetics. The Panel believes that the sizes of a substantial majority of the particles of aerosol and other spray products are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation, and thus, droplets/particles from cosmetic products would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel considered other data available to characterize the potential for *Eucalyptus globulus*-derived ingredients to cause systemic toxicity, irritation, sensitization, reproductive and developmental toxicity, and genotoxicity. They noted the lack of systemic toxicity at high doses in acute oral exposure studies (in contrast to old case reports), minimal or no

irritation or sensitization in tests of dermal exposure at relevant concentrations, and the absence of genotoxicity in multiple assays. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

Conclusion

The Expert Panel for Cosmetic Ingredient Safety concluded that the following ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be nonsensitizing:

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

* Not reported to be in current use. If this ingredient were to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to others in this group.

Author's Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1620 L Street, NW, Suite 1200, Washington, DC 20036, USA.

Author Contributions

The articles in this supplement were sponsored by the Cosmetic Ingredient Review.

Declaration of Conflicting Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The articles in this supplement were sponsored by the Cosmetic Ingredient Review. The Cosmetic Ingredient Review is financially supported by the Personal Care Products Council.

ORCID iD

Lillian C. Becker https://orcid.org/0000-0001-8281-1007

References

1. Nikitakis J, Lange B (eds). Web-Based Ingredient Dictionary (wINCI). http://webdictionary.personalcarecouncil.org/jsp/Home.jsp. Washington, DC. Last Updated 2017. Date Accessed 5-2-2017.
2. Goossens A. Cosmetic Contact Allergens. *Multidisciplinary Digital Publishing Institute: Cosmetics*. 2016;3(5):1-11.
3. Hagvall L, Karlberg AT, Christensson JB. Contact allergy to air-exposed geraniol: clinical observations and report of 14 cases. *Contact Dermatitis*. 2012;67(1):20-27.
4. Hagvall L, Karlberg AT, Christensson JB. Finding the optimal patch test material and test concentration to detect contact allergy to geraniol. *Contact Dermatitis*. 2013;68(4):224-231.
5. Nijkamp MM, Bokkers BGH, Bakker MI, Ezendam J, Delmaar JEQuantitative risk assessment of the aggregate dermal exposure to the sensitizing fragrance geraniol in personal care products and household cleaning agents. *Regul Toxicol Pharmacol*. 2015;73(1):9-18.
6. Tisserand R, Young R. *Essential Oil Safety*. 2 ed. Edinburgh, UK: Churchill Livingstone, Elsevier, 2014.
7. World Health Organization (WHO). WHO monographs on selected medicinal plants, Vol. 2. http://apps.who.int/medicinedocs/pdf/s4927e/s4927e.pdf. Geneva. Last Updated 1999.
8. Shah G, Kaur M, Singh PS, et al. Pharmacognostic parameters of *Eucalyptus globulus* leaves. *Phcog J*. 2012;4(24):38-43.
9. Bergfeld WF, Belsito DV, Klaassen CD, et al. *Safety Assessment of Phytosterols as Used in Cosmetics*. Washington, DC: Cosmetic Ingredient Review. 2013. pp. 1-23.
10. European Chemicals Agency (ECHA). *Eucalyptus Globulus, Ext*. http://echa.europa.eu/registration-dossier/-/registered-dossier/14864. European Chemicals Agency (ECHA). Last Updated 5-28-2017. Date Accessed 7-10-0017.
11. International Program of Chemical Safety (INCHEM). *Eucalyptus Oil*. http://www.inchem.org/documents/pims/pharm/pim031.htm#PartTitle:1.NAME. Last Updated 1998. Date Accessed 9-5-2017.
12. European Medicines Agency (EMA). *Assessment Report on* Eucalytus *[sic]* Globulus *labil.,* Eucalyptus Polybractea *R.T. Baker And/or* Eucalyptus Smithii *R.T. Baker, Aetheroleum*. London, United Kingdom: European Medicines Agency. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2013/07/WC500147006.pdf. Date Accessed 7-13-2017. Report No. EMA/HMPC/307782/2012. pp. 1-38.
13. Vuong QV, Chalmers AC, Jyoti Bhuyan D, Bowyer MC, Scarlett CJ. Botanical, phytochemical, and anticancer properties of the *Eucalyptus* species. *Chem Biodivers*. 2015;12(6):907-924.
14. U.S. National Plant Germplasm System. Taxon: Eucalyptus Globulus *Labill*. http://npgsweb.ars-grin.gov/gringlobal/taxonomydetail.aspx?id=15919. Last Updated 3-13-2017. Date Accessed 7-10-2017.
15. *British Pharmacopoeia 2008*. 5 ed. London: British Parmacopoeia Commission, 2008.
16. Saveyn A, Steppe K, Ubierna N, Dawson TEWoody tissue photosynthesis and its contribution to trunk growth and bud

development in young plants. *Plant Cell Environ*. 2010;33(11): 1949-1958.
17. Santos RL. *The Eucalyptus of California; Seeds of Good or Seeds of Evil? [pamphlet]*. Denair, CA: Alley-Cass Publications; 1997.
18. Eyles A, Pinkard EA, O'Grady AP, Worledge D, Warren CR. Role of corticular photosynthesis following defoliation in *Eucalyptus globulus*. *Plant Cell Environ*. 2009;32(8): 1004-1014.
19. Kaur G, Mohiuddin I, Aulakh J. An approach on phytochemistry and pharmacological studies of Eucalyptus globulus plant parts. *Res J Mater Sci*. 2017;5(4):1-9.
20. Boukhatem MN, Ferhat MA, Kameli A, Saidi F, Walid K, Mohamed SB. Quality assessment of the essential oil from *Eucalyptus globulus* Labill of Blida (Algeria) origin. *Int Lett Chem Phys Astron*. 2014;36(3):303-315.
21. Boelens M. Essential oils and aroma chemicals from Euclayptus Globlulus Labill. *Perfum Flavor*. 1984;9(December/January): 2-14.
22. Personal Care Products Council. 12-14-2017. *Eucalyptus Globulus Leaf Extract*. Unpublished data submitted by Personal Care Products Council.
23. Song A, Wang Y, Liu Y. Study on the chemical constituents of the essential oil of the leaves of *Eucalyptus globulus* Labill from China. *Asian Journal of Traditional Medicines*. 2009;4(4): 134-140.
24. Subramanian P, Gebrekidan A, Nigussie K. Yeild, contents and chemical composition variations in the essential oils of different *Eucalyptus globulus* trees from Tigray, Northern Ethiopia. *J Pharmaceut Biomed Sci*. 2012;17(11):1-6.
25. Matura M, Skõld M, Bõrje A, et al. Not only oxidized R-(+)- but also S-(-)-limonene is a common cause of contact allergy in dermatitis patients in Europe. *Contact Dermatitis*. 2006;55(5): 274-279.
26. Bickers D, Calow P, Greim H, et al. A toxicologic and dermatologic assessment of linalool and related esters when used as fragrance ingredients. *Food Chem Toxicol*. 2003; 41(7):919-942.
27. Duke JA. *Handbook of Phytochmical Constituents of GRAS Herbs and Other Economic Plants*. Boca Raton, FL: CRC Press, 1992.
28. National Toxicology Program (NTP). NTP technical report on the toxicology and carcinogenesis studies of β-myrcene (CAS No. 123-35-3) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC: National Institutes of Health. 2010. http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr557.pdf. Report No. 11-5898. 169.
29. Roe FJ, Field WE. Chronic toxicity of essential oils and certain other products of natural origin. *Food Cosmet Toxicol*. 1965; 3(2):311-323.
30. Homburger F, Boger E. The carcinogenicity of essential oils, flavors, and spices: A review. *Cancer Res*. 1968;28(11): 2372-2374.
31. National Toxicology Program (NTP). NTP Techinacal Report on the toxicity studies of α-pinene (CAS No. 80-56-8) administered by inhalation to F344/N rats and B6C3F1/N mice. Research Triangle Park, NC: National Toxicology Program (NTP. 2016. http://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox081_508.pdf. Report No. 81. pp. 1-119.
32. Harwood M, Danielewska-Nikiel B, Borzelleca JF, Flamm GW, Williams GM, Lines TC. A critical review of the data related to the safety of quercetin and lack of evidene of *in vivo* toxicity, including lack of genotoxic/carcinogenic properties. *Food Chem Toxicol*. 2007;45(11):2179-2205.
33. Poginsky B, Westendorf N, Prosenc N, et al. St. John's wort (*Hypericum perforatum* L.). Genotoxicity induced by quercetin content. *Dtsch Apoth Ztg (DAZ)*. 1988;128(26):1364-1366.
34. International Fragrance Association (IFRA). *IFRA Standards*. 2017. http://www.ifraorg.org/en-us/standards-library. Date Accessed 1-30-2017.
35. Extracts N. 2017. *Specification Technical Data Sheet NE Tasmanian Blue Gum Extract Cosmetic*. Unpublished data submitted by Personal Care Products Council.
36. Extracts N. 2017. *Safety Data Sheet: NE Tasmanian Blue Gum Extract*. Unpublished data submitted by Personal Care Products Council.
37. Anonymous. 2-2-2018. *Eucalyptus Globulus Leaf Extract: Summary Specification Information*. Unpublished data submitted by Personal Care Products Council.
38. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). *Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients*. College Park, MD: 2018. Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 3 2018; received February 5 2018).
39. Personal Care Products Council. 2-20-2018. Updated Concentration of Use by FDA Product Category: Eucalyptus globulus-Derived Ingredients. Unpublished data submitted by Personal Care Products Council.
40. Johnsen MA. The Influence of Particle Size. *Spray Technol Mark*. 2004;14(11):24-27.
41. Rothe H. Special aspects of cosmetic spray safety evaluation. 2011. Unpublished information presented to the 26 September CIR Expert Panel. Washington D.C.
42. Bremmer HJ, Prud'homme de Lodder LCH, van Engelen JGM. *Cosmetics Fact Sheet: To Assess the Risks for the Consumer*; Updated version for ConsExpo 4. 2006. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.
43. Rothe H, Fautz R, Gerber E, et al. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 2011;205(2):97-104. PM: 21669261.
44. United States Pharmacopeial Convention. *The United States Pharmacopeia, the National Formulary*. 27 ed. Rockville, MD, USA: United States Pharmacopeial Convention, 2009.
45. Food and Drug Administration (FDA). Cosmetics Program; Import and domestic. Chapter: 29. In: *Food and Drug Administration Compliance Program Guidance Manual*. 2016: 1-43.

46. European Commission. *CosIng Database: Following Cosmetic Regulation No. 1223*/2009. http://ec.europa.eu/growth/tools-databases/cosing/. Last Updated 2015. Date Accessed 7-12-2017.
47. European Commission Scientific Committee on Food. *Opinion of the Scientific Committee on Food on Euclalyptol. Brussel, Belgium*: European Commission Health & Consumer Protection Directorate-General. 2002. http://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out126_en.pdf. Date Accessed 9-19-2017. Report No. SCF/CS/FLAV/FLAVOUR/20 ADD2 Final. pp. 1-10.
48. Health Canada. *Natural Health Products; Aromatherapy - Essential Oils*. 2015. http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=aromatherap&lang=eng. Date Accessed 1-19-2017.pp. 1-14.
49. Karpanen TJ, Conway BR, Worthington T, Hilton AC, Elliott TSJ, Lambert PA. Enhanced chlorhexidine skin penetration with eucalyptus oil. *BMC Infect Dis*. 2010;10:278.
50. Shen T, Xu H, Weng W, Zhang J. Development of a reservoir-type transdermal delivery system containing eucalyptus oil for tetramethylpyrazine. *Drug Deliv*. 2013;20(1):19-24.
51. Amrish C, Kumar SP. Transdermal delivery of ketorolac. *Yakugaku Zasshi*. 2009;129(3):373-379.
52. AbDullah D, Ping QN, Liu GJ. Enhancing effect of essential oils on the penetration of 5-fluorouracil through rat skin. *Acta Parmaceutica Sinica*. 1996;31(3):214-221.
53. Scientific Committee on Food. *Opinion of the Scientific Committee on Food on Eucalyptol*. http://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out126_en.pdf. Bruxelles/Brussel, Belgium. Last Updated 2002. Date Accessed 9-19-2017.
54. Opdyke D. Fragrance raw materials monographs: Eucalyptol. *Food Cosmet Toxicol*. 1975;13(1):105-106.
55. Bhowal M, Gopal M. Eucalyptol: Safety and phamacological profile. *RGUHS Journal of Phamaceutical Sciences*. 2015;5(4)-125.
56. Kovar KA, Gropper B, Friess D, Ammon HP. Blood levels of 1,8-cineole and locomotor activity of mice after inhalation and oral administration of rosemary oil. *Planta Med*. 1987;53(4):315-318.
57. Gebremickael A, Gebru G, Debella A, Addis G. Acute and sub-chronic oral toxicity evaluation of Eucalyptus globulus essential oil-water emulsion in mice. *J Cytol Histol*. 2017;08(3):1-7.
58. Hu Z, Feng R, Xiang F, et al. Acute and subchronic toxicity as well as evaluation of safety pharmacology of eucalyptus oil-water emulsions. *Int J Clin Exp Med*. 2014;7(12):4835-4845.
59. Shalaby S, El-Din M, Abo-Donia S, et al. Toxicological affects of essential oils from eucalyptus *Eucalyptus globules* and clove *Eugenia caryophyllus* on albino rats. *Pol J Environ Stud*. 2011;20(2):429-434.
60. Boyd EM, Sheppard EP. The effect of steam inhalation of volatile oils on the output and composition of respiratory tract fluid. *J Pharmacol Exp Ther*. 1968;163(1):250-256.
61. Bastos VPD, Gomes AS, Lima FJB, et al. Inhaled 1,8-cineole reduces inflammatory parameters in airways of ovalbumin-challenged Guinea pigs. *Basic Clin Pharmacol Toxicol*. 2011;108(1):34-39.
62. Alzergy A, Mohamed N, Itia A. Toxicity of aqueous extract of *Eucalyptus* in Swice [sic] albino mice. *Suez Canal Veterinary Mdicine Journal (SCVMJ)*. 2010;15(1):199-214.
63. Arise R, Malomo S, Adebayo J, et al. Effects of aqeous extract of *Eucalyptus globulus* on lipid peroxication and selected enzymes of rat liver. *J Med Plants Res*. 2009;3(2):077-081.
64. Dhibi S, Mbarki S, Elfeki A, Hfaiedh N. *Eucalyptus globulus* extract protects upon acetaminophen-induced kidney damages in male rat. *Bosn J Basic Med Sci*. 2014;14(2):99-104.
65. Roe FJ, Palmer AK, Worden AN, Van Abbe NJ. Safety evaluation of toothpaste containing chloroform I. Long-term studies in mice. *J Environ Pathol Toxicol*. 1979;2(3):799-819.
66. European Chemicals Agency (ECHA). *Cineole*. http://echa.europa.eu/registration-dossier/-/registered-dossier/13231/1. European Chemicals Agency (ECHA). Last Updated 9-26-2017. Date Accessed 10-19-2017.
67. Opdyke D. Fragrance raw materials monographs: Eucalyptus oil. *Food Cosmet Toxicol*. 1975;13(1):107-108.
68. Sharp DW The sensitization potential of some perfume ingredients tested using a modified Draize procedure. *Toxicology*. 1978;9(3):261-271.
69. Research Testing Laboratories Incorporated. 1980. *Human Subject Patch Test Study: Schwartz-Peck Prophetic Patch and Draize-Shelanski Repeat Insult Test of a Skin Cream Containing 0.1% Eucalyptus Oil*. Unpublished data submitted by Personal Care Products Council.
70. TKL Research Inc. 2010. *Human Repeated Insult Patch Test with Challenge (Lipstick Containing 0.5% Eucalyptus Globulus Leaf Oil)*. Unpublished data submitted by Personal Care Products Council.
71. Placzek M, Frömel W, Eberlein B, Gilbertz KP, Przybilla B. Evaluation of phototoxic properties of fragrances. *Acta Derm Venereol*. 2007;87(4):312-316.
72. Uter W, Schmidt E, Geier J, Lessmann H, Schnuch A, Frosch P. Contact allergy to essential oils: Current patch test results (2000-2008) from the Information Network of Departments of Dermatology (IVDK). *Contact Dermatitis*. 2010;63(5):277-283.
73. Nardelli A, Drieghe J, Claes L, Boey L, Goossens A. Fragrance allergens in "specific" cosmetic products. *Contact Dermatitis*. 2011;64(4):212-219.
74. Rudzki E, Grzywa Z. Allergy to perfume mixture. *Contact Dermatitis*. 1986;15(2):115-116.
75. Guin JD. Use of consumer product ingredients for patch testing. *Dermatitis*. 2005;16(2):71-77.
76. Rudzki E, Grzywa Z, Bruo WS. Sensitivity to 35 essential oils. *Contact Dermatitis*. 1976;2(4):196-200.
77. Rudzki E, Grzywa Z. Balsam of Peru as screening agent for essential oils sensitivity. *Dermatol*. 1977;155(2):115-121.
78. Tibballs J. Clinical effects and management of eucalyptus oil ingestion in infants and young children. *Med J Aust*. 1995;163(4):177-180.

79. Darben T, Cominos B, Lee CT. Topical eucalyptus oil poisoning. *Australas J Dermatol*. 1998;39(4):265-267.
80. Kartal D, Kartal L, Çinar S, Borlu M. Allergic contact dermatitis caused by both eucalyptus oil and spruce oil. *Int J Med Pharm Case Reports*. 2016;7(2):1-3.
81. Selvaag E, Holm J-Ø, Thune P. Allergic contact dermatitis in an aroma therapist with multiple sensitizations to essential oils. *Contact Dermatitis*. 1995;33(5):354-355.
82. Sherry E, Boeck H, Warnke PH. Topical application of a new formulation of eucalyptus oil phytochemical clears methicillin-resistant *Staphylococcus aureus* infection. *Am J Infect Control*. 2001;29(5):346.
83. Spoerke DG, Vandenberg SA, Smolinske SC, Kulig K, Rumack BH. Eucalyptus oil: 14 cases of exposure. *Vet Hum Toxicol*. 1989;31(2):166-168.
84. Vilaplana J, Romaguera C. Allergic contact dermatitis due to eucalyptol in an anti-inflammatory cream. *Contact Dermatitis*. 2000;43(2):118.
85. Craig JO. Poisoning by the volatile oils in childhood. *Arch Dis Child*. 1953;28(142):475-483.
86. Foggie WE. Eucalyptus oil poisoning. *Br Med J*. 1911; 1(February 18, 2616):359-360.
87. Kumar KJ, Sonnathi S, Anitha C, SanthoshkuMar M. Eucalyptus oil poisoning. *Toxicol Int*. 2015;22(1):170-171.
88. Patel S, Wiggins J. Eucalyptus oil poisoning. *Arch Dis Child*. 1980;55(5):405-406.
89. Huggins JT, Kaplan A, Martin-Harris B, Sahn SA. Eucalyptus as a specific irritant causing vocal cord dysfunction. *Ann Allergy Asthma Immunol*. 2004;93(3):299-303.
90. Melis K, Bochner A, Janssens G, Bochner A. Accidental nasal eucalyptol and menthol instillation. *Eur J Pediatr*. 1989;148(8): 786-787.
91. Anonymous. 2011. *Certificate of Analysis Australian Eucalyptus Oil*. Unpublished data submitted by Personal Care Products Council.
92. Wetter DA, Yiannias JA, Prakash AV, Davis MDP, Farmer SA, el-Azhary RA. Results of patch testing to personal care product allergens in a standard series and a supplemental cosmetic series: An analysis of 945 patients from the Mayo Clinic Contact Dermatitis Group, 2000-2007. *J Am Acad Dermatol*. 2010;63(5):789-798.