
Safety Assessment of *Salvia officinalis* (Sage)-Derived Ingredients as Used in Cosmetics

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ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 12 *Salvia officinalis* (sage)-derived ingredients as used in cosmetic formulations. These ingredients are most commonly reported to function as skin conditioning agents and fragrance 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. With *Salvia officinalis* (sage)-derived ingredients, the Panel was concerned about terpenes as potential sensitizers. Industry should use current good manufacturing practices to minimize impurities. The Panel reviewed data relevant to the safety of these ingredients in cosmetic formulations, and concluded that 6 of the ingredients (those derived from the leaves and the oil) are safe in cosmetics in the present practices of use and concentrations described in this safety assessment when formulated to be non-sensitizing, and that the data are insufficient to make a determination that the remaining 6 ingredients are safe under the intended conditions of use in cosmetic formulations.

INTRODUCTION

This assessment reviews the safety of 12 *Salvia officinalis* (sage)-derived ingredients as used in cosmetic formulations:

Salvia Officinalis (Sage) Extract	Salvia Officinalis (Sage) Leaf Oil
Salvia Officinalis (Sage) Flower/Leaf/Stem Extract	Salvia Officinalis (Sage) Leaf Powder
Salvia Officinalis (Sage) Flower/Leaf/Stem Juice	Salvia Officinalis (Sage) Leaf Water
Salvia Officinalis (Sage) Flower/Leaf/Stem Water	Salvia Officinalis (Sage) Oil
Salvia Officinalis (Sage) Leaf	Salvia Officinalis (Sage) Root Extract
Salvia Officinalis (Sage) Leaf Extract	Salvia Officinalis (Sage) Water

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), various functions are reported for these ingredients, with skin-conditioning agent and fragrance ingredient being the most common; other reported functions include as an antioxidant, oral care agent, a flavoring agent, and exfoliant (Table 1).¹ No cosmetic function is reported for *Salvia Officinalis* (Sage) Leaf.

The Panel does not typically review ingredients that function only as fragrance ingredients, because, as fragrances, the evaluation of the safety of these ingredients is the purview of the Research Institute for Fragrance Materials (RIFM). *Salvia Officinalis* (Sage) Flower/Leaf/Stem Water and *Salvia Officinalis* (Sage) Water are reported to function only as fragrance ingredients in cosmetics, according to the wINCI *Dictionary* (see Table 1). Although RIFM published a monograph on Sage Oil, Dalmatian in 1979,² it appears the sage ingredients are not currently scheduled for review by RIFM; thus, the Panel is reviewing the safety of these ingredients.

These ingredients are all derived from the same species, and have therefore been grouped together in this assessment. *Salvia officinalis* may contain hundreds of constituents, some of which have the potential to cause toxic effects. For example, terpenes have the potential to cause dermal sensitization.³ In this assessment, the Panel is reviewing the potential toxicity of each of *Salvia officinalis*-derived ingredients as a whole, complex substance; toxicity from single components may not predict the potential toxicity of botanical ingredients.

The leaf ingredients reviewed in this safety assessment may be consumed as food, and daily exposure from food would result in much larger systemic exposures than those from use in cosmetic products. Although oral studies are included herein, the primary focus of this safety assessment is on the potential for effects from topical exposure to these ingredients as used in cosmetics.

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 and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (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 industry, as well as by other interested parties.

Much of the data included in this safety assessment is described on the European Chemicals Agency (ECHA) website⁴ and in the 2016 European Medicines Agency (EMA) monographs on *Salvia officinalis*.^{5,6} Please note that the ECHA website and EMA monographs provide summaries of information from the industry and toxicological studies, and it is those summary data that are reported in this safety assessment when ECHA and EMA are cited. The CAS No. 84082-79-1 referenced in the ECHA dossier is generic, and corresponds to several of the ingredients in this report. However, based on the definition for this substance in ECHA, these data were deemed to refer to the *Salvia Officinalis* (Sage) Oil ingredient, and have been described as such, when cited in this report.

The cosmetic ingredient names, according to the *Dictionary*, are written as listed above, without italics. In many of the published studies, it is not known how the substance being tested compares to the cosmetic ingredient. Therefore, if it is not known whether the chemicals being discussed are cosmetic ingredients, the test substances will be identified by the standard

taxonomic practice of using italics to identify genus and species (i.e., *Salvia officinalis* extract). However, if it is known that the substance is a cosmetic ingredient, the International Nomenclature Committee (INC) terminology (i.e., title case and no italics) “*Salvia Officinalis...*” (e.g., *Salvia Officinalis* (Sage) Extract) will be used. When referring to the plant from which these ingredients are derived, the standard scientific practice of using italics will be followed (i.e., *Salvia officinalis*).

CHEMISTRY

Definition and Plant Identification

The definitions of the 12 *Salvia officinalis* (sage)-derived ingredients reviewed in this assessment are presented in Table 1.¹ All of the ingredients included in this assessment have the generic CAS No. 84082-79-1; however, both *Salvia Officinalis* (Sage) Leaf Oil and *Salvia Officinalis* (Sage) Oil also have the CAS No. 8022-56-8 (generic).

Generically, the root is defined as a plant organ that lacks leaves and nodes, is usually underground, and absorbs and transports water and nutrients.¹ The flower is defined as the reproductive shoot in flowering plants, and is usually composed of sepals, petals, stamens, and pistil(s). The stem is defined as a slender or elongated structure, which supports a plant, fungus, or plant organ. The leaves are defined as the flattened photosynthetic organs of a plant, which are attached to the plant stems.

Salvia officinalis is a plant in the Lamiaceae (i.e., mint) family and Nepotoideae subfamily.⁷ Commonly referred to as sage, or Dalmatian sage, *Salvia officinalis* is native to the Mediterranean and Middle Eastern regions, and is cultivated throughout the Americas and Europe, including, Spain, Italy, Yugoslavia, Greece, Albania, Argentina, Germany, France, Malta, Turkey, England, and Canada.^{8,9} It is a medium-size perennial evergreen herb, which grows as a bush, having a quadrangular base, with many branches.⁹ The plant can grow up to 60 - 70 cm in height. The leaves are arranged in an opposite and whorled pattern, and are oblong, 2.5 - 6.0 cm long, wrinkled, and light green to silver gray in color. *Salvia officinalis* blooms in early summer, and has blue, white, or purple flowers that have two lips, are up to 3 cm long, and are attached in whorls on short, upright flower spikes.

Chemical Properties

Ingredients with reported properties (only 3) are provided as liquids, with densities comparable to water. A summary of chemical properties described for these *Salvia officinalis* (sage)-derived ingredients are provided in Table 2.

Method of Manufacture

Some of the methods below are general to the processing of *Salvia officinalis* (sage), and it is unknown if they apply to cosmetic ingredient manufacturing.

Salvia Officinalis (Sage) Flower/Leaf/Stem Extract

In the preparation of an aqueous *Salvia officinalis* leaf extract, 1 g of dried aerial *Salvia officinalis* was added to 200 ml of boiling water, and the solution was left to stand at room temperature for 5 min, filtered under reduced pressure, frozen, and lyophilized.¹⁰ A preparation of a methanolic *Salvia officinalis* extract was then obtained by stirring a 1 g sample of dried aerial *Salvia officinalis* with 30 ml of a methanol/water (80:20 v/v) solvent at 25 °C and 150 rpm for 1 h, and then filtering the extract. A second step extraction was obtained with an additional 30 ml of the solvent; extracts from both steps were combined, evaporated at 35 °C under reduced pressure, and further lyophilized. The lyophilized methanolic *Salvia officinalis* extracts were re-dissolved in methanol/water (80:20 v/v); the aqueous *Salvia officinalis* extracts were re-dissolved in water. The resulting stock solutions contained a 20 mg/ml concentration of *Salvia officinalis* extract.

Salvia Officinalis (Sage) Flower/Leaf/Stem Juice

Salvia Officinalis (Sage) Flower/Leaf/Stem Juice is the juice expressed from the flowers, leaves, and stems of *Salvia officinalis*.¹

Salvia Officinalis (Sage) Flower/Leaf/Stem Water

Salvia Officinalis (Sage) Flower/Leaf/Stem Water is the aqueous solution of the steam distillate obtained from the flowers, leaves, and stems of *Salvia officinalis*.¹

Salvia Officinalis (Sage) Leaf Extract

One supplier described a trade mixture containing *Salvia Officinalis* (Sage) Leaf Extract (dry extract between 1.8 – 3%), propylene glycol, and water as a hydroglycolic extract obtained from *Salvia officinalis* leaves, via controlled extraction using propylene glycol and water.¹¹ In another method of manufacture for *Salvia Officinalis* (Sage) Leaf Extract, described by a supplier, dried leaves are extracted with eluent(s), such as water, butylene glycol, glycerin, propylene glycol, or carthamus tinctorius (safflower) seed oil, under appropriate temperature conditions, to yield a concentrate.¹² This concentrate is then blended with the desired diluent(s) and is preserved to yield the final ingredient. Both the intermediate concentrate and the final ingredient are evaluated for physiochemical properties, contaminants, and specification requirements.

A supplier provided 5 methods of manufacture for 5 separate *Salvia Officinalis* (Sage) Leaf Extracts.¹³ In general, dried *Salvia officinalis* leaves were extracted with either a 30% or 90 vol% ethanolic solution or with a 50 vol% 1,3-butylene glycolic solution, and filtered to produce a filtrate. The resulting filtrate (sometimes called a concentrate) went through a

sedimentation process, and was filtered and adjusted as needed, prior to packaging. In one of the described methods, the extract concentrate was dissolved in squalane prior to sedimentation.

Salvia Officinalis (Sage) Oil

A *Salvia officinalis* oil sample was prepared by first drying and grinding the aerial parts of *Salvia officinalis* to yield 250 g of powder.¹⁴ The powder was subject to hydrodistillation for 3 h using a Clevenger apparatus; the eluted oil was dried over anhydrous sodium sulfate and preserved in a sealed vial at 4 °C.

Salvia Officinalis (Sage) Leaf Water

Salvia Officinalis (Sage) Leaf Water was described by a supplier as an aqueous extract obtained by steam distillation of the *Salvia officinalis* leaves.¹⁵

Salvia Officinalis (Sage) Water

Salvia Officinalis (Sage) Water is the aqueous solution of the steam distillate obtained from *Salvia officinalis*.¹

Composition and Impurities

The determination of individual constituents and natural content in *Salvia officinalis*-derived ingredients varies considerably depending on the extraction solvent and method, part of the plant, growth stage, and time of harvest.¹⁶⁻²⁰

The European Food Safety Authority issued a recommended maximum residue level of 20 mg/kg ametoctradin, a fungicide, in *Salvia officinalis*.^{21,22} In an analysis of pesticide residues, commercial samples of *Salvia officinalis* in Poland were found to have boscalid, chlorpyrifos, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane, dimethoate, and indoxacarb in negligible amounts (0.02 - 0.05 mg/kg).²³ The researchers concluded that the presence of these contaminants in herbal infusions would be minimal.

Salvia Officinalis (Sage) Extract

An aqueous extract of *Salvia officinalis* was reported to have a total phenolic compound content of 158.9 ± 38.0 µg gallic acid equivalents.²⁴

Salvia Officinalis (Sage) Leaf Extract

Theoretical calculations made by a supplier indicate that a trade mixture of propylene glycol, water, and Salvia Officinalis (Sage) Leaf Extract contains less than 10 ppm geraniol, less than 125 ppm limonene, and less than 225 ppm linalool.¹¹ Borneol, cineol, luteolin, apigenin, caffeic acid, and rosmarinic acid were identified as being present in this extract.

In an industry assessment conducted on the concentrate in an alcohol base, no heavy metals or pesticide residues were detected in Salvia Officinalis (Sage) Leaf Extract.¹² Similarly, testing the concentrate of Salvia Officinalis (Sage) Leaf Extract, in an alcohol base, for the 26 allergens identified by the European Union yielded a universal threshold of < 10 ppm – 0.001%.¹²

Flavonoids and tannins were the primary components identified in 4 Salvia Officinalis (Sage) Leaf Extracts, prepared using 30% or 90% ethanol, or 50% 1,3-butylene glycolic solution.¹³ The levels of heavy metals and arsenic found in 4 of these Salvia Officinalis (Sage) Leaf Extract samples were not more than 20 ppm and 2 ppm, respectively. In a fifth sample of Salvia Officinalis (Sage) Leaf Extract, in which the intermediate concentrate was dissolved in squalane, the primary components were also flavonoids and tannins, and detected heavy metal and arsenic levels were no more than 10 ppm and 2 ppm, respectively.

Salvia Officinalis (Sage) Leaf Water

Theoretical calculations made by a supplier, indicate that a Salvia Officinalis (Sage) Leaf Water contains less than 10 ppm geraniol, less than 125 ppm limonene and less than 225 ppm linalool.¹⁵ The presence of borneol was also identified in this ingredient.

Salvia Officinalis (Sage) Leaf Oil

The main classes of constituents identified in an Albanian sample of *Salvia officinalis* leaf oil were monoterpene hydrocarbons (21.5%), oxygenated monoterpenoids (66.5%), sesquiterpene hydrocarbons (9.4%), and oxygenated sesquiterpenoids (2.4%).²⁵ The major components in this *Salvia officinalis* leaf oil sample were α - and β -thujone, of which α -thujone was proportionally higher.

Salvia Officinalis (Sage) Oil

According to the EMA monograph, the principal components of *Salvia officinalis* oil are thujone, 1,8-cineole, and camphor; in 25 different commercial sources of sage leaves, camphor levels varied from 7 - 50%.⁵ The main classes of constituents in *Salvia officinalis* oil are identified as terpenoids, hydroxycinnamic acid derivatives, flavonoids, phenolic glycosides, and polysaccharides. According to the 49th Amendment of the International Fragrance Association (IFRA) standards, in the absence of analytical data, thujone is expected to occur naturally from 2-10% in *Salvia officinalis* oleoresin and from 8 – 33% in *Salvia officinalis* oil.²⁶

An essential oil of *Salvia officinalis* is described as being obtained from leaves, flowers, and stalks by steam distillation.⁴ The major components in this oil were identified as 1-isopropyl-4-methylbicyclo[3.1.0]hexan-3-one; DL-bornan-2-one; cineole; (1*S*, 4*S*, 5*R*)-4-methyl-1-(1-methylethyl)bicyclo[3.1.0]hexan-3-one; camphene; humulene; pin-2(3)-ene; caryophyllene; (1*S*-endo)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol; pin-2(10)-ene; *p*-mentha-1,4-diene; dipentene; L-born-2-yl acetate; and 7-methyl-3-methyleneocta-1,6-diene.

The major components of a *Salvia officinalis* oil from Iran were identified as α -thujene (13.96%), α -pinene (12.91%), and 1,8-cineole (22.91%).¹⁴ Percent composition of both *Salvia officinalis* leaf oil and *Salvia officinalis* oil samples is provided in Table 3.

USE Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics, and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21 CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application, and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2022 VCRP survey data, *Salvia Officinalis* (Sage) Leaf Extract is reported to have the greatest frequency of use; it is reported to be used in 211 formulations, 114 of which are rinse-off formulations²⁷ (Table 4). The other ingredients have 105 or fewer reported uses. The results of the concentration of use survey conducted by the Council in 2020 indicate *Salvia Officinalis* (Sage) Leaf Extract also has the highest reported concentration of use; it is used at up to 0.38% in other skin care preparations.^{28,29} The 5 *Salvia officinalis* (sage)-derived ingredients which are not reported to be in use are listed in Table 5.

A few of the *Salvia officinalis* (sage)-derived ingredients are reported to be used in products applied near the eye, such as *Salvia Officinalis* (Sage) Leaf at up to 0.0001% in eye lotions, and in products that can result in incidental ingestion (e.g., *Salvia Officinalis* (Sage) Oil at up to 0.011% in dentifrices). Additionally, some of the ingredients are used in formulations that could come in contact with mucous membranes, such as *Salvia Officinalis* (Sage) Oil at up to 0.02% in bath soaps and detergent.

Furthermore, some of the *Salvia officinalis* (sage)-derived ingredients are used in cosmetic spray formulations, and could possibly be inhaled. For example, *Salvia Officinalis* (Sage) Leaf Extract is reported to be used in pump and aerosol hair sprays at up to 0.0001% and 0.002%, respectively, *Salvia Officinalis* (Sage) Extract is reported to be used in underarm deodorant spray at up to 0.0011%, and *Salvia Officinalis* (Sage) Leaf Oil is reported to be used in pump spray suntan formulations at up to 0.012%. *Salvia Officinalis* (Sage) Leaf Extract is reported to be used in 1 face powder formulation (concentration of use not reported). In practice, as stated in the Panel's respiratory exposure resource document (<https://www.cir-safety.org/cir-findings>), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable. However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

Although products containing some of these ingredients may be marketed for use with airbrush technology, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients, and without consumer habits and practices data related to this use technology, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

All of the ingredients named in the report are not restricted from use in any way under the rules governing cosmetic products in the European Union.³⁰ However, IFRA limits the levels of thujone in finished products, depending on the product category, ranging from 0.0053% to 9.5%.²⁶

Non-Cosmetic

Salvia officinalis L. is generally recognized as safe (GRAS) as an essential oil, oleoresin (solvent-free), and natural extractive (including distillates), and, as a spice, natural seasoning and flavoring for human consumption, according to the US FDA [21CFR § 182.20; 21CFR § 182.10, respectively]. *Salvia officinalis L.* is also GRAS as a spice and other natural seasoning and flavoring for use in animal feed [21CFR § 582.10]. Additionally, *Salvia officinalis* oil is listed as a GRAS flavoring substance by the Flavor Extract Manufacturers Association.² Also, sage oil may have previously been used as an active ingredient in over-the-counter, astringent drug products; however, the FDA citation states that there are inadequate data to establish general recognition of the safety and effectiveness of the ingredient for this specified use [21CFR § 310.545]. The *Salvia officinalis* plant is a common potherb; *Salvia officinalis* leaves are typically used for flavoring meat, fish, and poultry dishes.³¹

According to a 2016 EMA herbal monograph of *Salvia officinalis L.*, folium, an aqueous infusion of *Salvia officinalis* is applied to the skin in traditional medicine for the relief of minor inflammation.⁶ The monograph also describes *Salvia officinalis* being consumed orally as a dry/liquid extract or tincture, for the treatment of heartburn, bloating, excessive sweating, and relief of inflammation of the mouth or throat. Most medicinal uses of *Salvia officinalis* products in Europe are marketed in varied forms, at a daily dose of 1.5 - 2.5 g/d.⁵ In Spain, a dry extract of *Salvia officinalis* is marketed for the treatment of excessive sweating at a dose of 360 mg/d (equivalent to 500 - 800 mg of dried *Salvia officinalis* leaves). Pure *Salvia officinalis* oil and extract consumption is contraindicated during pregnancy, due to its abortifacient and emmenagogic properties.⁵

TOXICOKINETIC STUDIES

No relevant toxicokinetic studies on *Salvia officinalis* (sage)-derived ingredients were found in the published literature, and unpublished data were not submitted. In general, toxicokinetic data are not expected to be found on botanical ingredients because each botanical ingredient is a complex mixture of constituents.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute dermal and oral toxicity studies summarized below are described in Table 6.

The acute dermal LD₅₀ values for *Salvia officinalis* (Sage) Leaf Extract, eluted in 50% 1,3-butylene glycolic solution, and *Salvia officinalis* oil or *Salvia officinalis* leaf oil were determined to be > 2000 mg/kg in mice and > 5000 mg/kg in rabbits, respectively.^{2,13} No visible signs of toxicity were observed in groups of 6 female Swiss mice administered a single oral dose of up to 5000 mg/kg hydroalcoholic *Salvia officinalis* extract.³² No visible signs of toxicity were observed. All animals in the 5000 mg/kg group showed piloerection and diarrhea lasting up to 3 h after treatment. One animal from the 5000 mg/kg group died before 48 h. The acute oral LD₅₀ in female Swiss mice was extrapolated to be 44,760 mg/kg. In one study, a *Salvia officinalis* leaf and stem extract was determined to be non-toxic when administered to 6 female albino rats at the maximum dose of 2000 mg/kg bw.³³ The acute oral LD₅₀ of *Salvia officinalis* oil or *Salvia officinalis* leaf oil was determined to be 2600 mg/kg bw in rats.² Groups of 10 male Wistar rats were administered an oral, undiluted, dose of *Salvia officinalis* oil at 1290, 2020, 3200, or 5000 mg/kg bw.⁴ One animal died from the 1290 mg/kg group, 4 died from the 2020 mg/kg group, 7 died from the 3200 mg/kg group, and 9 animals died from the 5000 mg/kg group. The calculated LD₅₀ was determined to be 2600 mg/kg bw.

Short-Term Toxicity Studies

Oral

Salvia officinalis (Sage) Oil or Salvia officinalis (Sage) Leaf Oil

In an 8-wk study using groups of 5 white rats (sex and strain not specified), a daily dose of 250 mg/kg bw *Salvia officinalis* oil was well tolerated when given by oral administration.⁵ Upon increase of the daily dose to 500 mg/kg bw/d, convulsions occurred in some animals. Upon increase to 1000 mg/kg bw/d, most animals died, and all animals died when the dose was increased to 1250 mg/kg bw/d (timing and duration of all 3 dose increases not provided). The no-observed-adverse-effect-level (NOAEL) of *Salvia officinalis* oil was determined to be 250 mg/kg bw/d, under the conditions of this study.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Details of the developmental and reproductive toxicity studies summarized below are described in Table 7.

Groups of 7 female Wistar rats were administered either distilled water or 30 mg/kg bw/d hydroalcoholic extract (70% ethanol) of *Salvia officinalis*, orally, for 30 d.³⁴ No significant differences in blood estradiol or progesterone were observed, and a decrease in the duration of estrous cycles in *Salvia officinalis* extract-treated rats was not statistically significant. An increased number of alveolar buds and lobules in the whole mount slides, as well as an increase in the number and diameter of ducts in the histological sections of rats treated with *Salvia officinalis* extract, were statistically significant. In a study

evaluating the estrogenic effects of up to 200 mg/kg bw, orally administered, ethanolic *Salvia officinalis* leaf and stem extract in immature ovariectomized female rats for 7 d, vaginal smears collected on day 8 exhibited varying estrus cycle phases, compared to controls, and significant increases in the percentage of positively stained cells were seen in the uterine tissue of rats treated with 100 and 200 mg/kg bw leaf and stem extract.³³ Similarly, rats treated with the *Salvia officinalis* leaf extract exhibited a significant dose-dependent increase in uterine weights. Twenty-four female ICR mice received a daily dose of 0.25% *Salvia officinalis* oil (equivalent to 375 mg/kg/d), in rodent feed, for 14 d.³⁵ A significant decrease in embryo cell distribution, according to nucleus number, was observed in dams which consumed *Salvia officinalis* oil (until day 4 of gestation), compared to control females fed with 1% edible soya oil. Dam weights and the proportion of dead cells in embryos were not affected.

GENOTOXICITY STUDIES

Details of the in vitro genotoxicity studies summarized below are described in Table 8.

Salvia Officinalis (Sage) Leaf Extract, eluted in 50% 1,3-butylene glycolic solution, was not genotoxic in a reverse mutation test using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or *Escherichia coli* WP2 uvrA at up to 5000 µg/0.1 ml/plate.¹³ *Salvia officinalis* oil was not found genotoxic when tested at concentrations up to 5000 µg/plate, in two bacterial reverse mutation assays.^{4,36} *Salvia officinalis* oil was not found genotoxic in a chromosome aberration test at doses up to 0.15 mg/ml.³⁷ In one Ames test, *Salvia officinalis* oil, at doses of 91, 183, or 457 µg/plate, was shown to significantly inhibit bacterial growth, however, was not considered genotoxic.³⁸

ANTI-MUTAGENICITY STUDIES

In Vitro

Salvia Officinalis (Sage) Extract

The anti-mutagenic potential of *Salvia officinalis* extract was tested in 3 groups of 5 male C3H mice.³⁹ Animals were first intraperitoneally dosed with 1 mg/kg of a positive mutagen, mitomycin C (MMC), and then with 25, 50, or 100 µl/kg *Salvia officinalis* extract. Bone marrow was extracted 24 h after treatment and tested for aberrations. Treatment with 25 and 50 µl/kg *Salvia officinalis* extract immediately after MMC exposure significantly decreased the frequency of cells in metaphase with chromosome aberrations, relative to cells only treated with MMC. However, the 100 µl/kg dose of *Salvia officinalis* extract was shown to be cytotoxic by itself, and when administered after MMC (confirmed in a preliminary test).

CARCINOGENICITY STUDIES

No relevant carcinogenicity studies on *Salvia officinalis* (sage)-derived ingredients were found in the published literature, and unpublished data were not submitted.

ANTI-CARCINOGENICITY STUDIES

Animal

Salvia Officinalis (Sage) Leaf Extract

In a tumorigenesis study, 20 female Wistar rats, which were previously induced with dimethyl-benzanthracene to develop breast cancer, were orally dosed with 3 mg/kg/d of an hydroalcoholic *Salvia officinalis* leaf extract for 6 mo.⁴⁰ The control group consisted of 8 rats which received 3 ml of sunflower oil, every 2 d, for 3 consecutive wk. Cancer stage and progression was analyzed throughout the course of the study. Cancerous lobule counts were significantly lower in the *Salvia officinalis* leaf extract treated group, compared to controls in the fourth and sixth mo of treatment.

OTHER RELEVANT STUDIES

Cytotoxicity

Salvia Officinalis (Sage) Leaf Oil

The cytotoxic activity of *Salvia officinalis* leaf oil in various cancer cell lines was determined using half maximal inhibitory concentration (IC₅₀) values.⁴¹ The IC₅₀ values of *Salvia officinalis* leaf oil were 554.5 ± 1.5 µg/ml against the MCF-7 breast cancer cell line, 394.6 ± 1.4 µg/ml, against the HCT-116 colon cancer cell line, and 207.5 ± 0.8 µg/ml against the RAW264.7 murine macrophage cell line.

Salvia Officinalis (Sage) Oil

Salvia officinalis oil was determined to have an IC₅₀ value of 367.43 µg/ml ± 1.5 µg/ml against a C32 human melanoma cell line, and an IC₅₀ of 108.70 ± 1.2 against an ACHN renal carcinoma cell line.⁴²

DERMAL IRRITATION AND SENSITIZATION STUDIES

The dermal irritation and sensitization studies summarized below are described in Table 9.

In an in vitro skin corrosion reconstituted human epidermis (Rhe) test, performed according to Organization for Economic Cooperation and Development (OECD) test guideline (TG) 431, 50 µl *Salvia officinalis* oil did not cause irritation to Rhe tissue surfaces, epiCS[®].⁴ In another in vitro skin irritation Rhe test, performed in accordance with OECD TG 439, 16 µl of *Salvia officinalis* oil was applied neat to 3 separate, 0.50 cm² reconstituted human epidermis tissue surfaces (EpiSkin SA, RHE/S/17); cell viability was measured in a MTT assay.⁴ Mean percent viability of the treated tissues was 2.1%, compared to 2.9% in the positive control replicates exposed to 5% sodium dodecyl sulfate. Under these test conditions, the test substance was classified as “irritating to the skin” or “corrosive to the skin”. Undiluted and 10% *Salvia officinalis* (Sage) Leaf Extract (eluted in 50% 1,3-butylene glycolic solution) were not irritating when applied to rabbit skin.¹³ *Salvia officinalis* oil, or *Salvia officinalis* leaf oil was moderately irritating when applied under occlusion to intact, or abraded rabbit skin for 24 h.² One irritation reaction occurred in a 24-h patch test of undiluted *Salvia officinalis* oil, or *Salvia officinalis* leaf oil, using 20 subjects;^{2,43} In another study, *Salvia officinalis* oil, or *Salvia officinalis* leaf oil, tested at 8% in petrolatum, did not produce irritation in a 48-h occlusive patch test of human subjects.² A product containing 0.005% *Salvia officinalis* (Sage) Leaf Extract, applied at a 1% dilution in distilled water, and a product containing 0.03% *Salvia officinalis* (Sage) Oil were not irritating or sensitizing in two separate occlusive human repeated insult patch tests (HRIPT) completed in 53 subjects.^{44,45} A maximization test was carried out on 25 subjects, using *Salvia officinalis* oil, or *Salvia officinalis* leaf oil, tested at a concentration of 8% in petrolatum.² The test article was deemed non-sensitizing.

OCULAR IRRITATION STUDIES

In Vitro

Salvia officinalis (Sage) Oil

The potential of *Salvia officinalis* oil to cause eye irritation was evaluated in a reconstructed human cornea-like epithelium test.⁴ The test was performed in accordance with OECD TG 492, using an EpiOcular™ three-dimensional human cornea model. Fifty µl of the undiluted test article was applied to 2 living tissue models (duplicate runs), pretreated with DPBS, for 30 min. The treated tissue was then washed out with DPBS and post-incubated under normal medium and culture conditions for 2 h. Cell viability was measured via an MTT assay; positive controls were treated with methyl acetate. In the first test, viability was 60.34%, compared to 24.44% in positive controls. In the second test, viability was 80.96% compared to 18.36% in the positive controls. The test substance was not considered an ocular irritant.

CLINICAL STUDIES

Case Reports

Salvia officinalis (Sage) Extract

An 83-yr old woman presented with swelling and redness of the lips and the surrounding area, followed by tightness and a burning sensation, which persisted for 3 mo.⁴⁶ The allergic reaction was attributed to a lip balm she had previously used. The subject was patch tested with the European baseline, cosmetic and bakery series, and with the suspected lip balm. On day 2 and 4, positive reaction readings were noted only for the lip balm. The subject was then patch tested with manufacturer-supplied *Salvia officinalis* extract and polygonum, each separately in water and in petrolatum. Positive reactions only occurred to *Salvia officinalis* extract. Patch tests of the lip balm, *Salvia officinalis* extract, and polygonum were negative in 20 other subjects.

Salvia officinalis (Sage) Oil

A 65-yr old healthy woman, a professional aromatherapist, with no prior history of skin disease, presented with eczema on her arms and upper trunk, which later spread to the legs, face, and hands.⁴⁷ The hand eczema became chronic and was associated with handling household cleansers, sealing wax and paints, as well as customary dilution of essential oils. The subject tested positive to a fragrance mix (++) in the European standard series, and to lemongrass oil (++) , neroli oil (+), and peppermint oil (+), in a perfume series. When patch tested with personally-used essential oils, diluted in petrolatum at 1% and 5%, the subject tested positive to 17 out of 20 oils, of which *Salvia officinalis* was one (++, at both concentrations). The subject recalled lemongrass being the first oil she had used in aromatherapy, which the researchers surmised had induced primary sensitization, and lead to later development of dermatitis to the other essential oils.

SUMMARY

According to the *Dictionary*, various functions are reported for these 12 *Salvia officinalis* (sage)-derived ingredients as used in cosmetics, with skin-conditioning agent and fragrance ingredient being the most common. Other reported functions include as an antioxidant, oral care agent, flavoring agent, and exfoliant. *Salvia officinalis* (Sage) Leaf Extract is reported to have the greatest frequency of use, in 211 formulations, more than half (114) are rinse-offs. The highest reported concentration of use amongst these ingredients is for *Salvia officinalis* (Sage) Leaf Extract, at up to 0.38% in other skin preparations.

The acute dermal LD₅₀ of *Salvia officinalis* (Sage) Leaf Extract, eluted in 50% 1,3-butylene glycolic solution, was determined to be > 2000 mg/kg in 5 mice. The acute dermal LD₅₀ of *Salvia officinalis* oil, or *Salvia officinalis* leaf oil (plant

part not stated), was determined to be > 5000 mg/kg in rabbits. Of 6 female Swiss mice administered a single oral dose of 5, 50, 500, or 5000 mg/kg bw hydroalcoholic *Salvia officinalis* extract, one mouse in the 5000 mg/kg group died; the acute oral LD₅₀ was extrapolated to be 44,760 mg/kg. No mortality or signs of toxicity were observed in 6 female albino rats dosed with up to 2000 mg/kg bw of an ethanolic *Salvia officinalis* leaf and stem extract; the extract was considered non-toxic at the maximum dose of 2000 mg/kg bw. The acute oral LD₅₀ of *Salvia officinalis* oil or *Salvia officinalis* leaf oil in rats was determined to be 2600 mg/kg bw. Lethargy was observed in all groups of 10 male Wistar rats administered an undiluted oral dose of 1290, 2020, 3200, or 5000 mg/kg bw *Salvia officinalis* oil. One animal from the 1290 mg/kg group, 4 animals from the 2020 mg/kg group, 7 animals from the 3200 mg/kg group, and 9 animals from the 5000 mg/kg group died. The calculated LD₅₀ was determined to be 2600 mg/kg bw.

In an 8-wk study, white rats were administered a progressively increasing oral dose of *Salvia officinalis* oil (250, 500, 1000, or 1250 mg/kg bw/d), convulsions and mortality were observed with increasing dosage. The NOAEL was determined to be 250 mg/kg bw/d, under the study conditions.

A group of 7 female Wistar rats administered a daily oral dose, for 30 d, of 30 mg/kg bw/d hydroalcoholic *Salvia officinalis* extract did not exhibit significant differences in hormone levels or estrous cycle lengths, as compared to controls administered distilled water. However, upon examination, a significant increase in alveolar buds, lobules, and the diameter of mammary ducts was observed. Groups of 6 immature, ovariectomized rats orally dosed with 50, 100 or 200 mg/kg bw *Salvia officinalis* leaf and stem extract for 7 d exhibited significant increases in positive staining for estrogen receptors in the 100 mg/kg group. Serum levels of LH and FSH were also significantly lower (41.7% and 49.1%) in the 200 mg/kg group, compared to ovariectomized controls. In a reproductive toxicity study with 13 gravid female ICR mice, a 14-d diet containing 0.25% *Salvia officinalis* oil caused significant decreases in embryo cell distribution, collected on day 4 of gestation, according to nucleus number.

Salvia officinalis oil and *Salvia officinalis* (Sage) Leaf Extract were not found genotoxic when tested at concentrations of up to 5000 µg/plate in bacterial mutation assays; *Salvia officinalis* oil was not genotoxic at up to 0.15 mg/ml in a chromosome aberration test. When tested at doses of up to 457 µg/plate, *Salvia officinalis* oil significantly inhibited bacterial growth, however, it was not considered genotoxic, in an Ames test. C3H mice intraperitoneally dosed with up to 100 µl/kg *Salvia officinalis* extract, after exposure to MMC, had a significant decrease in the frequency of cells in metaphase with chromosome aberrations. The 100 µl/kg dose of *Salvia officinalis* extract exhibited cytotoxicity, even in the absence of MMC.

Twenty female Wistar rats, that were induced with dimethyl-benzanthracene to develop breast cancer, saw significant reductions in cancerous lobules during the fourth and sixth month of being orally dosed with 3 mg/kg/d of an hydroalcoholic *Salvia officinalis* leaf extract for 6 mo, compared to sunflower oil controls. *Salvia officinalis* leaf oil yielded IC₅₀ values of 554.5 ± 1.5 µg/ml, 394.6 ± 1.4 µg/ml, and 207.5 ± 0.8 µg/ml against breast cancer, colon cancer, and murine macrophage cell lines, respectively. *Salvia officinalis* oil was determined to have an IC₅₀ of 367.45 ± 1.5 µg/ml and 108.70 ± 1.2 µg/ml against C32 human melanoma and ACHN renal carcinoma cell lines, respectively.

A 50 µl dose of undiluted *Salvia officinalis* oil did not cause irritation in an in vitro Rhe test. In another in vitro Rhe test, the mean percent cell viability of tissues treated with 16 µl of undiluted *Salvia officinalis* oil was 2.1%, compared to 2.9% in positive controls exposed to 5% sodium dodecyl sulfate; the test substance was classified as a skin irritant or dermally corrosive. Undiluted and 10% *Salvia officinalis* (Sage) Leaf Extract, eluted in 50% 1,3-butylene glycolic solution, were not irritating to rabbit skin. Undiluted *Salvia officinalis* oil, or *Salvia officinalis* leaf oil, was moderately irritating when applied to intact and abraded rabbit skin under occlusion for 24 h. One irritation reaction occurred in a 24-h patch test of undiluted *Salvia officinalis* oil, or leaf oil, using 20 subjects. The sensitization potential of a product containing 0.005% *Salvia officinalis* (Sage) Leaf Extract, tested at a 1% dilution in distilled water and of a body lotion containing 0.03% *Salvia officinalis* (Sage) Oil was tested in 2 separate occlusive HRIPTs completed in 53 subjects; no adverse reactions were observed, and the test substances were deemed non-irritating and non-sensitizing. No irritation or sensitization was observed when 8% *Salvia officinalis* oil, or leaf oil, in petrolatum was tested via a 48-h occlusive patch test or a maximization test using 25 subjects, respectively. *Salvia officinalis* oil was not considered an ocular irritant when tested at a dose of 50 µl in an EpiOcular™ model.

An 83-yr old woman had positive reactions in a patch test to a lip balm containing *Salvia officinalis* extract. Upon separate patch testing with two of the manufacturer-supplied ingredients, *Salvia officinalis* extract and polygonum, in water and in petrolatum, positive reactions only occurred to *Salvia officinalis* extract. Patch test results for the lip balm, *Salvia officinalis* extract, and polygonum were negative in 20 other subjects. A 65-yr old woman, with no prior skin disease, presented with eczema on her arms, upper trunk, legs, face, and hands; when patch tested with personally-used essential oils diluted in petrolatum, the subject tested positive to *Salvia officinalis* oil at 1% and 5%. Primary sensitization was attributed to lemongrass oil, and subsequent dermatitis to the frequent use of other essential oils as an aromatherapist.

DISCUSSION

This assessment reviews the safety of 12 *Salvia officinalis* (sage)-derived ingredients as used in cosmetic formulations. The Panel concluded that the data are sufficient for determining the safety of 6 ingredients, i.e., those ingredients derived

from the leaves and the oil, due to negative human irritation and sensitization data for these ingredients. The Panel, alternately, discussed that additional data would be needed to determine the safety of the remaining 6 ingredients that are derived from the whole plant, flowers, stems, and roots. Specifically, the Panel acknowledged the need for a 28-day dermal toxicity study of *Salvia Officinalis* (Sage) Flower/Leaf/Stem Extract, *Salvia Officinalis* (Sage) Root Extract, or the whole plant; dependent on the results of that study, additional toxicity data may be needed.

The Panel noted the GRAS status and historical food uses of *Salvia officinalis* (sage)-derived ingredients, especially *Salvia officinalis* leaves, and agreed that systemic exposures from food would be much higher than those from cosmetic use. Additionally, the Panel was reassured by the 250 mg/kg/d NOEL seen in an 8-wk study of rats orally dosed with *Salvia officinalis* oil. The Panel also acknowledged negative human irritation and sensitization data for leaf-derived and oil ingredients, which further supports the safety of these ingredients.

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 *Salvia officinalis* (sage)-derived ingredients, the Panel was concerned about the presence of terpenes/terpenoids in cosmetics, which have dermal sensitization potential. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

The Panel also expressed concern about pesticide residues, heavy metals, and other plant species that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (e.g., *Salvia Officinalis* (Sage) Leaf Oil is used at up to 0.012% in pump spray suntan formulations, *Salvia Officinalis* (Sage) Extract is used at up to 0.0011% in underarm deodorant spray, and *Salvia Officinalis* (Sage) Leaf Extract has 1 confirmed use in face powders (concentration of use not reported)). Inhalation toxicity data were not available. However, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. 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>.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 6 *Salvia officinalis* (sage)-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:

Salvia Officinalis (Sage) Leaf	Salvia Officinalis (Sage) Leaf Powder*
Salvia Officinalis (Sage) Leaf Extract	Salvia Officinalis (Sage) Leaf Water
Salvia Officinalis (Sage) Leaf Oil	Salvia Officinalis (Sage) Oil

**Not reported to be in current use. Were this ingredient not in current use 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.*

The Panel also concluded that the available data are insufficient to make a determination that the following 6 ingredients are safe under the intended conditions of use in cosmetic formulations:

Salvia Officinalis (Sage) Extract	Salvia Officinalis (Sage) Flower/Leaf/Stem Water**
Salvia Officinalis (Sage) Flower/Leaf/Stem Extract**	Salvia Officinalis (Sage) Root Extract**
Salvia Officinalis (Sage) Flower/Leaf/Stem Juice**	Salvia Officinalis (Sage) Water

*** There are currently no uses reported for these ingredients.*

TABLES

Table 1: Definitions and functions of *Salvia officinalis* (sage) - derived ingredients¹

Ingredient/CAS No.	Definition	Function
Salvia Officinalis (Sage) Extract 84082-79-1 (generic)	Salvia Officinalis (Sage) Extract is the extract of the whole plant, <i>Salvia officinalis</i> .	Skin-conditioning agents- miscellaneous
Salvia Officinalis (Sage) Flower/Leaf/Stem Extract 84082-79-1 (generic)	Salvia Officinalis (Sage) Flower/Leaf/Stem Extract is the extract of the flowers, leaves, and stems of <i>Salvia officinalis</i> .	Fragrance ingredients; Skin-conditioning agents - miscellaneous
Salvia Officinalis (Sage) Flower/Leaf/Stem Juice 84082-79-1 (generic)	Salvia Officinalis (Sage) Flower/Leaf/Stem Juice is the juice expressed from the flowers, leaves, and stems of <i>Salvia officinalis</i> .	Antioxidants
Salvia Officinalis (Sage) Flower/Leaf/Stem Water 84082-79-1 (generic)	Salvia Officinalis (Sage) Flower/Leaf/Stem Water is the aqueous solution of the steam distillate obtained from the flowers, leaves, and stems of <i>Salvia officinalis</i> .	Fragrance ingredients
Salvia Officinalis (Sage) Leaf 84082-79-1 (generic)	Salvia Officinalis (Sage) Leaf are the leaves of <i>Salvia officinalis</i> .	not reported
Salvia Officinalis (Sage) Leaf Extract 84082-79-1 (generic)	Salvia Officinalis (Sage) Leaf Extract is the extract of the leaves of <i>Salvia officinalis</i> .	Oral care agents; Skin-conditioning agents- miscellaneous
Salvia Officinalis (Sage) Leaf Oil 84082-79 -1 (generic) 8022-56-8	Salvia Officinalis (Sage) Leaf Oil is the volatile oil obtained from the leaves of <i>Salvia officinalis</i> .	Flavoring agents; Fragrance ingredients; Skin-conditioning agents - miscellaneous
Salvia Officinalis (Sage) Leaf Powder 84082-79-1 (generic)	Salvia Officinalis (Sage) Leaf Powder is the powder obtained from the dried ground leaves of <i>Salvia officinalis</i> .	Exfoliants
Salvia Officinalis (Sage) Leaf Water 84082-79-1 (generic)	Salvia Officinalis (Sage) Water is an aqueous solution of the steam distillate obtained from the leaves of <i>Salvia officinalis</i> .	Fragrance ingredients; Skin-conditioning agents - miscellaneous
Salvia Officinalis (Sage) Oil 84082-79-1 (generic) 8022-56-8	Salvia Officinalis (Sage) Oil is the essential oil derived from the herbal plant, <i>Salvia officinalis</i> .	Fragrance ingredients; Skin-conditioning agents- miscellaneous
Salvia Officinalis (Sage) Root Extract 84082-79-1 (generic)	Salvia Officinalis (Sage) Root Extract is the extract of the roots of <i>Salvia officinalis</i> .	Skin-conditioning agents- miscellaneous
Salvia Officinalis (Sage) Water 84082-79-1 (generic)	Salvia Officinalis (Sage) Water is an aqueous solution of the steam distillate obtained from <i>Salvia officinalis</i> .	Fragrance ingredients

Table 2. Chemical properties of *Salvia officinalis* (sage) – derived ingredients and a tradename mixture

Property	Value	Reference
Salvia Officinalis (Sage) Leaf Extract (aqueous)		
Physical Form	Liquid	12
Color	Medium to dark amber	12
Density (g/ml @ 25 °C)	0.99 – 1.02	12
Refractive Index (@ 25 °C)	1.320 – 1.3450	12
pH (@ 25 °C)	4 – 7	12
Solubility	In water	12
Salvia Officinalis (Sage) Leaf Extract (1.8 -3% dry extract, in a tradename mixture, containing propylene glycol and water)		
Physical Form	Liquid, with slight precipitate	11
Color	Brown to brown-orange	11
Density (g/ml)	1.045 – 1.058	11
Refractive Index (@ 20 °C)	1.410 – 1.420	11
Miscibility	In water and 50 % v/v alcohol	11
Non-miscibility	Mineral and vegetal oils	11
pH	4 - 5	11
Salvia Officinalis (Sage) Leaf Oil or Oil		
Physical Form	Liquid	4
Color	Light yellow to yellow	4
Density (g/ml @ 20 °C)	0.9153	4
Odor	Camphoraceous, herbal, spicy, floral, pine, thujone-like	48
Boiling Point (°C @ 1013 kPa)	189.3	4

Table 2. Chemical properties of *Salvia officinalis* (sage) – derived ingredients and a tradename mixture

Property	Value	Reference
	Salvia Officinalis (Sage) Leaf Water	
Physical Form	Liquid	15
Color	colorless	15
Density (g/ml @ 20°C)	0.999 – 1.002	15
Refractive Index	1.332 – 1.339	15
Miscibility	In water and 50% v/v alcohol	15
Non-miscibility	Mineral and vegetal oils	15
pH	4 – 6.5	15

Table 3. Composition of *Salvia officinalis* (sage) oils, measured via gas chromatography- mass spectrometry

Compound	Salvia officinalis leaf oil ²⁵	Salvia officinalis oil ¹⁴
	Percentage (%)	
<i>cis</i> -salvene	-- (not reported)	0.40
(<i>Z</i>)-salvene	0.2	--
(<i>E</i>)-salvene	trace	--
tricyclene	0.2	0.09
α -thujene	0.3	13.9
α -pinene	5.0	12.91
camphene	5.2	4.74
sabinene	0.1	--
<i>trans</i> -sabinene hydrate	--	0.13
β -pinene	4.1	5.93
β -thujene	--	8.91
1-octen-3-ol	trace	--
β -myrcene	--	0.69
myrcene	2.8	--
α -phellandrene	0.1	--
1-phellandrene	--	0.15
α -terpinene	0.5	0.31
α -terpinolene	--	0.20
<i>p</i> -cymene	0.6	--
limonene	1.5	--
1-napthalenepropanol	--	0.11
1,8-cineole	26.9	22.91
(<i>Z</i>)- β -ocimene	0.1	0.1
γ -terpinene	0.7	0.41
<i>cis</i> -sabinene hydrate	0.1	--
terpinolene	0.2	--
<i>p</i> -cymenene	trace	--
linalool	0.3	--
α - thujone	17.2	--
β - thujone	3.8	--
chrysanthenone	trace	--
3- <i>iso</i> -thujanol	trace	--
camphor	12.8	3.28
<i>neo-iso-3</i> -thujanol	trace	--
<i>trans</i> -pinocamphone	0.1	--
3- thujanol	0.2	--
borneol	1.2	6.18
δ - terpineol	0.4	--
terpinen-4-ol	0.5	--
α - gurjunene	--	0.1
α - terpineol	1.1	--
linalyl acetate	0.2	--
endobornyl acetate	--	0.77
bornyl acetate	1.1	0.39
<i>trans</i> -sabinyl acetate	0.1	--
<i>trans</i> -caryophyllene		7.41
2,3- pinanediol	trace	--
α - terpinyl acetate	0.6	--
α - copaene	0.1	--
β - caryophyllene	4.9	--
6-oxobornyl acetate	trace	--
α - maaliene	0.1	--

Table 3. Composition of *Salvia officinalis* (sage) oils, measured via gas chromatography- mass spectrometry

Compound	<i>Salvia officinalis</i> leaf oil ^{* 25}	<i>Salvia officinalis</i> oil ^{* 14}
Compound	Percentage (%)	
aromadendrene	0.4	0.56
myltayl-4 (12)-ene	trace	--
5-oxobornyl acetate	0.1	--
α - humulene	3.1	3.19
9- <i>epi</i> - β - caryophyllene	0.1	--
<i>trans</i> -cadinol 1(6)-4-diene	0.1	--
guaia-1(10)-11- diene	0.1	--
viridiflorene	0.3	--
δ - amorphene	0.1	--
δ - cadinene	0.1	0.24
Caryophyllene oxide	0.1	--
viridiflorol	2.0	3.08
humulene epoxide II	0.2	--
caryophylla-4(12),8(13)-dien-5 α -ol	0.1	--
manool	0.2	--

Table 4. Frequency (2022)²⁷ and concentration of use (2020)^{28,29} of *Salvia officinalis* (sage)-derived ingredients according to duration and exposure

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Salvia Officinalis (Sage) Extract		Salvia Officinalis (Sage) Leaf		Salvia Officinalis (Sage) Leaf Extract	
Totals*	70	0.00028-0.078	1	0.0001-0.1	211	0.000004-0.38
Duration of Use						
Leave-On	44	0.001-0.078	1	0.0001	95	0.0001-0.38
Rinse-Off	26	0.00028-0.01	NR	0.1	114	0.000004-0.08
Diluted for (Bath) Use	NR	NR	NR	NR	2	0.004
Exposure Type						
Eye Area	NR	NR	NR	0.0001	3	NR
Incidental Ingestion	3	NR	NR	NR	5	NR
Incidental Inhalation-Spray	14 ^a ; 21 ^b	0.02 ^b	NR	NR	1; 50 ^a ; 24 ^b	0.0001-0.002; 0.001-0.018 ^a
Incidental Inhalation-Powder	21 ^b	0.02 ^b	NR	NR	1; 24 ^b	NR
Dermal Contact	36	0.001-0.078	1	0.0001-0.1	140	0.0002-0.38
Deodorant (underarm)	1 ^a	Not spray: 0.001% Spray: 0.0011%	NR	NR	NR	NR
Hair - Non-Coloring	31	0.00028-0.003	NR	NR	51	0.000004-0.08
Hair-Coloring	NR	NR	NR	NR	15	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	4	0.0035-0.01	NR	NR	31	0.004-0.01
Baby Products	NR	NR	NR	NR	NR	NR
Totals*	2	0.0028-0.02	3	0.00071	105	0.000097-0.22
Duration of Use						
Leave-On	NR	0.0028-0.02	2	0.00071	69	0.012-0.22
Rinse Off	1	0.02	1	NR	30	0.000097-0.18
Diluted for (Bath) Use	1	NR	NR	NR	6	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	1	NR
Incidental Ingestion	1	NR	NR	NR	3	0.005-0.011
Incidental Inhalation-Spray	NR	0.012	1 ^a	0.00071 ^b	1; 30 ^a ; 15 ^b	0.005 ^a
Incidental Inhalation-Powder	NR	NR	NR	0.00071 ^b	15 ^b	0.22 ^c
Dermal Contact	1	0.0028-0.02	3	0.00071	88	0.0097-0.22
Deodorant (underarm)	NR	NR	1 ^a	NR	1 ^a	NR
Hair - Non-Coloring	NR	NR	NR	NR	14	0.000097-0.0049
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	NR	NR	NR	10	0.005-0.02
Baby Products	NR	NR	NR	NR	NR	NR
Totals*	1	NR				
Duration of Use						
Leave-On	1	NR				
Rinse-Off	NR	NR				
Diluted for (Bath) Use	NR	NR				
Exposure Type						
Eye Area	NR	NR				
Incidental Ingestion	NR	NR				
Incidental Inhalation-Spray	1 ^b	NR				
Incidental Inhalation-Powder	1 ^b	NR				
Dermal Contact	1	NR				
Deodorant (underarm)	NR	NR				
Hair - Non-Coloring	NR	NR				
Hair-Coloring	NR	NR				
Nail	NR	NR				
Mucous Membrane	NR	NR				
Baby Products	NR	NR				

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

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

^b Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories.

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

NR – not reported

Table 5. *Salvia officinalis* (sage) - derived ingredients not reported to be in use²⁷⁻²⁹

Salvia Officinalis (Sage) Flower/Leaf/Stem Extract
Salvia Officinalis (Sage) Flower/Leaf/Stem Juice
Salvia Officinalis (Sage) Flower/Leaf/Stem Water
Salvia Officinalis (Sage) Leaf Powder
Salvia Officinalis (Sage) Root Extract

Table 6. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD ₅₀ Results	Reference
DERMAL						
Salvia Officinalis (Sage) Leaf Extract	mice	5 mice	1, 3-butylene glycolic solution	50%	>2000 mg/kg	¹³
Salvia officinalis oil or Salvia officinalis leaf oil	rabbits	NR	NR	NR	>5000 mg/kg	²
ORAL						
Salvia officinalis extract	Female Swiss mice	6/group	Hydroalcoholic extract	5, 50, 500, or 5000 mg/kg	Extrapolated to be 44, 760 mg/kg. No visible signs of toxicity were observed. All animals in the 5000 mg/kg group showed piloerection and diarrhea lasting up to 3 h after treatment. One animal from the 5000 mg/kg group died before 48 h.	³²
Salvia officinalis leaf and stem extract	albino rats	6 females	Ethanol	1% v/v Tween 80 in distilled water (control), or 500 -2000 mg/kg bw test article. Animals were observed for symptoms of toxicity or mortality for 14 d.	The extract was considered non-toxic at the maximum dose of 2000 mg/kg bw. No mortality or signs or toxicity were observed over 14 d.	³³
Salvia officinalis oil or Salvia officinalis leaf oil	rats	NR	NR	NR	2600 mg/kg bw	²
Salvia officinalis oil	Male Wistar rats	10/group	none	1290, 2020, 3200, or 5000 mg/kg bw. Mortality was observed for up to 14 d after treatment, after which all surviving animals were killed.	Calculated to be 2600 mg/kg bw. One animal died from the 1290 mg/kg group, 4 died from the 2020 mg/kg group, 7 died from the 3200 mg/kg group, and 9 animals died from the 5000 mg/kg group. Lethargy was observed in all rats	⁴

Abbreviations: NR- not reported

Table 7. Developmental and reproductive toxicity studies

Test Article	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results	Reference
ORAL						
<i>Salvia officinalis</i> extract	7 female Wistar rats/group	70% ethanol	Distilled water or 30 mg/kg bw/d, via gavage for 30 d	Estrous cycle changes were monitored with daily vaginal smears. At the end of the observation period, animals in the estrus phase of the estrous cycle were dissected under deep anesthesia. Blood samples were taken to be analyzed in a hormonal assay. Right and left mammary glands from the pelvic region were excised, from which whole mount and formalin-fixed slides were prepared, respectively.	No significant differences in blood estradiol or progesterone were observed, and a decrease in the duration of estrous cycles in <i>Salvia officinalis</i> extract-treated rats was not statistically significant. An increased number of alveolar buds and lobules in the whole mount slides, as well as an increase in the number and diameter of ducts in the histological sections of rats treated with <i>Salvia officinalis</i> extract, were statistically significant.	³⁴
<i>Salvia officinalis</i> leaf and stem extract	6 female rats	ethanol	1% v/v Tween 80 in distilled water (controls) 50, 100, or 200 mg/kg bw/d, via gavage for 7 d	One control group was not ovariectomized, while a second control group served as ovariectomized controls; both control groups were administered 1% v/v Tween 80 in distilled water. An additional group was administered an i.p. dose of 1 µg/d of estradiol, as standard drug treatment. On day 8, vaginal smears were collected from all animals for evaluation of estrus cycle phase and blood samples were drawn to assess serum levels of luteinizing hormone and follicle-stimulating hormone. Then, after the animals were killed, the uteri underwent immunohistochemical staining for estrogen receptors, dissection to examine uterine histology, and were weighed to calculate relative uterus weights.	Vaginal smears from rats treated with the <i>Salvia officinalis</i> leaf and stem extract exhibited varying estrus cycle phases, compared to ovariectomized controls. Serum levels of LSH and FSH were also significantly reduced in the 200 mg/kg bw group (41.7% and 49.1%, respectively). While a decreased percentage of cells stained positively for estrogen receptors in the 50 mg/kg group (compared to the non-ovariectomized controls), significant increases in the percentage of positively stained cells were seen in the uterine tissue of rats treated with 100 and 200 mg/kg bw leaf and stem extract. Increased endometrial thickness, associated with stromal inflammation, was seen in both rats treated with estradiol and the <i>Salvia officinalis</i> leaf and stem extract, and dose-dependent increases in endometrial thickness, were seen in the latter group of treated rats, suggesting uterotrophic effects. Similarly, rats treated with the <i>Salvia officinalis</i> leaf extract exhibited a significant dose-dependent increase in uterine weights.	³³
<i>Salvia officinalis</i> oil	24 female ICR mice	rodent feed	0.25% (equivalent to 375 mg/kg/d), in diet, for 14 d	After the initial 2-wk period, 3 females were housed with 1 male for 8 d, to induce fertilization. Unfertilized dams were excluded. Post-mating, 13 fertilized females pretreated with <i>Salvia officinalis</i> oil were fed, ad libitum, a diet containing <i>Salvia officinalis</i> oil, while 13 control females were fed a diet with 1% edible soya oil (vehicle), till day 4 of gestation. Dams were killed on day 4 of gestation, and the embryos were recovered at the blastocyst stage of development and prepared for morphological analyses. The number and distribution of pre-implantation embryo nuclei, and the percentage of normal and dead cells, were measured as markers of growth and development.	A significant decrease in embryo cell distribution, according to nucleus number, was observed in dams which consumed <i>Salvia officinalis</i> oil. Dam weights and the proportion of dead cells in embryos were not affected.	³⁵

Abbreviations: FSH- follicle-stimulating hormone; ICR – Institute of Cancer Research; LH-luteinizing hormone

Table 8. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VITRO						
Salvia Officinalis Leaf Extract (50 vol% 1,3-butylene glycolic solution)	5000 µg/0.1 ml/plate	none specified	<i>Salmonella typhimurium</i> strains TA 98, TA 100, TA 1535, and TA1537 and <i>Escherichia coli</i> WP2uvrA	Bacterial reverse mutation assay	Not genotoxic	13
<i>Salvia officinalis</i> oil or <i>Salvia officinalis</i> leaf oil	Up to 5000 µg/plate; with and without metabolic activation	Paraffin oil	<i>S. typhimurium</i> strains TA 98, TA 100, TA 1535, TA 1537, and <i>E. coli</i> WP2	Bacterial reverse mutation assay, in accordance with OECD TG 471.	Not genotoxic	4
<i>Salvia officinalis</i> oil	91, 183, or 457 µg/plate, with and without metabolic activation	DMSO	<i>S. typhimurium</i> strains TA 98 and TA 100	Ames test	Not genotoxic. Significantly inhibited bacterial growth.	38
<i>Salvia officinalis</i> oil	0.25, 0.5, or 1 µl/plate	DMSO	<i>S. typhimurium</i> strains TA 98, TA 100, TA 1535, TA1537	Bacterial reverse mutation assay	Not genotoxic	36
<i>Salvia officinalis</i> oil	Up to 0.15 mg/ml	Ethanol	<i>S. typhimurium</i> strains TA92, TA 94, TA 98, TA 100, TA 1535, TA 1537	Chromosomal aberration test	Not genotoxic	37

Abbreviation: DMSO- dimethyl sulfoxide

Table 9. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
IN CHEMICO / IN VITRO STUDIES					
<i>Salvia officinalis</i> oil	50 µl	epiCS®	OECD TG 431. Skin corrosion test and MTT assay. Two separate tissue samples were exposed to the test article, applied neat, for 3 min and 1 h, and were then rinsed with DPBS after each exposure. Cell viability was measured in an MTT assay.	Not corrosive; mean percent cell viability of both tissue replicates were 100% and 39.83%, compared to 20.26% and 0% in positive control replicates.	4
<i>Salvia officinalis</i> oil	16 µl	EpiSkin SA	OECD TG 439. In vitro skin irritation test. Three separate tissue samples were exposed to the test article for 42 min, rinsed with DPBS, and incubated for 42 h in fresh medium. Cell viability was measured in an MTT assay.	Irritating or corrosive to the skin. The mean percent viability of treated tissue was 2.1% compared to 2.9% in the positive controls exposed to 5% sodium dodecyl sulfate	4
ANIMAL					
<i>Salvia officinalis</i> leaf extract	Undiluted, and 10%, in 50% 1,3-butylene glycolic solution	3 rabbits	NR	Not irritating	13
<i>Salvia officinalis</i> oil or <i>Salvia officinalis</i> leaf oil	NR	rabbits	24-h occlusive patch test, performed on intact and abraded rabbit skin. The test article was applied neat.	Moderately irritating	2
HUMAN					
<i>Salvia officinalis</i> oil or <i>Salvia officinalis</i> leaf oil	NR	20 subjects	24-h occlusive patch test. The test article was applied neat.	Not irritating. One irritation reaction occurred.	2,43
<i>Salvia officinalis</i> oil or <i>Salvia officinalis</i> leaf oil	8%, in petrolatum	NR	48-h occlusive patch test	Not irritating or sensitizing	2
Salvia Officinalis (Sage) Leaf Extract	0.2 ml; 1%, in water	53 subjects	HRIPT. Nine, 24-h applications of the test article were made to the back over a 3-wk induction period. After a 2-wk non-treatment period, a 24-h challenge application was made to a previously untreated site, and was scored after 24 and 72 h.	Not irritating or sensitizing	44
Sage Officinalis (Sage) Oil	0.1-0.15 g	53 subjects	HRIPT. Nine, 24-h applications of the test article were made to the back over a 3-wk induction period. After a 2-wk non-treatment period, a 24-h challenge application was made to a previously untreated site and was scored after 24 and 72 h.	Not irritating or sensitizing	45

Abbreviations: epiCS® - reconstituted human epidermis tissue surfaces; HRIPT – human repeated insult patch test; MTT - 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; OECD- Organization for Economic Cooperation and Development; TG – test guideline

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