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

Status:	Tentative Report for Public Comment
Release Date:	January 12, 2022
Panel Meeting Date:	March 7-8, 2022

All interested persons are provided 60 days from the above release date (i.e., March 13, 2022) to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to the Cosmetic Ingredient Review (CIR) will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Preethi S. Raj, M.Sc., Senior Scientific Analyst/ Writer, CIR.

1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088 ♢
cirinfo@cir-safety.org

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. The Panel noted 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 mainly 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*-derived ingredients as used in cosmetic formulations:

Salvia Officinalis (Sage) Extract
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
Salvia Officinalis (Sage) Leaf Extract
Salvia Officinalis (Sage) Leaf Oil
Salvia Officinalis (Sage) Leaf Powder
Salvia Officinalis (Sage) Leaf Water
Salvia Officinalis (Sage) Oil
Salvia Officinalis (Sage) Root 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 an 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). However, it appears that these ingredients have not been reviewed, and are not 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.[2] 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) website[3] and in the 2016 European Medicines Agency (EMA) monographs on *Salvia officinalis*.[4,5] 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 has 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.[6] 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.[7,8] It is a medium-size perennial evergreen herb, which grows as a bush, having a quadrangular base, with many branches.[8] 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

A summary of chemical properties described for *Salvia officinalis* (sage)-derived ingredients are provided in Table 2.

Salvia Officinalis (Sage) Leaf Extract

A supplier described a trade mixture containing Salvia Officinalis (Sage) Leaf Extract (dry extract between 1.8 – 3%), propylene glycol, and water as a brown to brown-orange translucent liquid, with slight precipitate.[9] The mixture was further described to be miscible in water and 50% v/v alcohol, non-miscible in mineral and vegetal oils, have a pH of 4 – 5, a refractive index of 1.410 – 1.420, and, at 20 °C, have a density of 1.045 – 1.058 g/cm^3.

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 *Saliva 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.[9] 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.[11] 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.[12] 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) Leaf Oil

Salvia Officinalis (Sage) Leaf Oil is the volatile oil obtained from the leaves of *Salvia officinalis*.[1]

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.[13] 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 Powder

Salvia Officinalis (Sage) Leaf Powder is the powder obtained from the dried ground leaves of *Salvia officinalis*.[1]

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.[14]

Salvia Officinalis (Sage) Root Extract

Salvia Officinalis (Sage) Root Extract is the extract of the roots of *Salvia officinalis*.[1]

Salvia Officinalis (Sage) Water

Salvia Officinalis (Sage) Water is the aqueous solution of the steam distillate obtained from the leaves of 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.[15-19]

The European Food Safety Authority issued a recommended maximum residue level of 20 mg/kg ametoctradin, a fungicide, in *Salvia officinalis*.[20,21] In an analysis of pesticide residues, commercial samples of *Salvia officinalis* in Poland were found to have boscalid, chlorpyrifos, 1,1,1-tricloro-2,2-*bis*(4-chlorophenyl)ethane, dimethoate, and indoxacarb in negligible amounts (0.02 - 0.05 mg/kg).[22] 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.[23]

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.[9] 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.[11] 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%.[11]

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.[12] 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.[14] 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%).[24] 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% .[4] The main classes of constituents in *Salvia officinalis* oil are identified as terpenoids, hydroxycinnamic acid derivatives, flavonoids, phenolic glycosides, and polysaccharides.

An essential oil of *Salvia officinalis* is described as being obtained from leaves, flowers, and stalks by steam distillation.[3] 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%).[13] 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 are 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. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2021 VCRP survey data, Salvia Officinalis (Sage) Leaf Extract is reported to have the greatest frequency of use; it is reported to be used in 213 formulations, 116 of which are rinse-off formulations[25] (Table 3). The other ingredients have 87 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.[26,27] Five *Salvia officinalis* (sage)–derived ingredients which are not reported to be in use are listed in Table 4.

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 at 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%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 μm, with propellant sprays yielding a greater fraction of droplets/particles < 10 μm compared with pump sprays.[28,29] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[30,31] 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.[30] 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.

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.[32] However, the 49th Amendment of the International Fragrance Association (IFRA) standard states that thujone is expected to occur naturally at 8 - 33% in *Salvia officinalis* oil and 2.5 - 10% in *Salvia officinalis* oleoresin, and can therefore be restricted if found at higher levels in these ingredients.[33] Furthermore, IFRA limits the levels of thujone in finished products, depending on the product category, ranging from 0.0053% in several skin contact products to 9.5% in products not intended for direct skin contact.

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.[34] 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.[35]

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.[5] 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.[4] In Spain, a dry extract of *Salvia officinalis* is marketed for the treatment of excessing 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.[4]

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

Dermal

Salvia Officinalis (Sage) Leaf Extract

The acute dermal LD_{50} of Salvia Officinalis (Sage) Leaf Extract, eluted in 50% 1,3-butylene glycolic solution, was determined to be > 2000 mg/kg in 5 mice.[12] No further details were provided.

Salvia Officinalis (Sage) Oil or Salvia Officinalis (Sage) Leaf Oil

The acute dermal LD_{50} of *Salvia officinalis* oil or *Salvia officinalis* leaf oil (unclear from source) was determined to be > 5000 mg/kg, in rabbits.[34] No further details were provided.

Oral

Salvia Officinalis (Sage) Extract

A single oral dose of an hydroalcoholic extract of *Salvia officinalis* was administered to groups of 6 female Swiss mice, at doses of 5, 50, 500, or 5000 mg/kg.[36] 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 LD_{50} in female Swiss mice was extrapolated to be 44,760 mg/kg.

Salvia Officinalis (Sage) Flower/Leaf/Stem Extract

Six female albino rats were administered a one-time dose of 1% v/v Tween 80 in distilled water (control), or 500 - 2000 mg/kg bw of an ethanolic *Salvia officinalis* leaf and stem extract.[37] Animals were observed for symptoms of toxicity or mortality for 14 d; the extract was considered not toxic at the maximum dose of 2000 mg/kg bw. No further details were provided.

Salvia Officinalis (Sage) Oil or Salvia Officinalis (Sage) Leaf Oil

The acute oral LD_{50} of *Salvia officinalis* oil or *Salvia officinalis* leaf oil (unclear from source) was determined to be 2600 mg/kg bw, in rats.[34] No further details were provided.

In an acute oral toxicity study, 4 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.[3] Mortality was observed for up to 14 d after treatment, after which all surviving animals were killed. 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. The calculated LD_{50} 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.[4] 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

Oral

Salvia Officinalis (Sage) Extract

Distilled water or 30 mg/kg bw/d hydroalcoholic extract (70% ethanol) of *Salvia officinalis* was administered orally, via gavage, to groups of 7 female Wistar rats for 30 d.[38] 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 *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.

Sage Officinalis (Sage) Flower/Leaf/Stem Extract

The possible estrogenic effects of an ethanolic *Salvia officinalis* leaf and stem extract were examined in groups of 6 immature ovariectomized female rats for 7 d.[37] 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, while treatment animals were dosed with 50, 100, or 200 mg/kg bw *Salvia officinalis* leaf and stem extract, via gavage. 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 (LH) and follicle-stimulating hormone (FSH). 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 *Salvia officinalis* 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 *Salvia officinalis* leaf and stem extract, and dose-dependent increases in endometrial thickness, were seen in the latter group of treated rats, suggesting uterotrophic effects. Similarly, treatment with the *Salvia officinalis* leaf extract exhibited a significant dose-dependent increase in uterine weights.

Salvia Officinalis (Sage) Oil

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.[39] After this 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 *Salvia officinalis* oil were fed, *ad libitum,* a diet containing *Salvia officinalis* 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 *Salvia officinalis* 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 5.

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.[12] *Salvia officinalis* oil was not found genotoxic when tested at doses up to 5000 µg/plate, in two bacterial reverse mutation assays.[3,40] *Salvia officinalis* oil was not found genotoxic in a chromosome aberration test at doses

up to 0.15 mg/ml.[41] In one Ames test, *Salvia officinalis* oil, in doses of 91, 183, or 457 µg, was shown to significantly inhibit bacterial growth, however, was not considered genotoxic.[42]

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.[43] 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.[44] 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 (IC_{50}) values.[45] The IC_{50} 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 IC_{50} value of 367.43 µg/ml ± 1.5 µg/ml against a C32 human melanoma cell line, and an IC_{50} of 108.70 ± 1.2 against an ACHN renal carcinoma cell line.[46]

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

In Vitro

Salvia Officinalis (Sage) Oil

The in vitro skin corrosion reconstructed human epidermis (Rhe) test was performed, in accordance with Organisation for Economic Cooperation and Development (OECD) test guideline (TG) 431, using 2 separate, 0.60 cm^2, reconstituted human epidermis tissue surfaces (epiCS®).[3] Tissues were exposed to 50 µl of undiluted *Salvia officinalis* oil for 3 min and 1 h, and were rinsed with 20 ml of Dulbecco's phosphate-buffered saline (DPBS) after each exposure. Cell viability was measured via a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) colorimetric assay. Mean percent cell viability, of both test tissue replicates, were 100% and 39.83%, compared to 20.26% and 0% in positive control replicates exposed to 8 N potassium hydroxide. Based on these results, the test substance was not considered corrosive to skin.

Another in vitro skin irritation Rhe test was performed, in accordance with OECD TG 439, using 3 separate, 0.50 cm^2 reconstituted human epidermis tissue surfaces (EpiSkin SA, RHE/S/17).[3] Tissues were exposed to 16 µl of undiluted *Salvia officinalis* oil for 42 min, rinsed with 25 ml of DPBS, and incubated for 42 h in fresh medium. Cell viability was measured in a MTT colorimetric assay. The mean percent viability of 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".

Animal

Salvia Officinalis (Sage) Leaf Extract

Undiluted and 10% Salvia Officinalis (Sage) Leaf Extract, eluted in 50% 1,3-butylene glycolic solution, was non-irritating to the skin of 3 rabbits.[12] No further details provided.

Salvia Officinalis (Sage) Oil or Salvia Officinalis (Sage) Leaf Oil

Undiluted *Salvia officinalis* oil, or *Salvia officinalis* leaf oil (unclear from source), was moderately irritating when applied to intact, or abraded, rabbit skin, under occlusion for 24 h.[34] No further details provided.

Human

Salvia Officinalis (Sage) Oil or Salvia Officinalis (Sage) Leaf Oil

One irritation reaction occurred in a 24-h patch test of undiluted *Salvia officinalis* oil, or *Salvia officinalis* leaf oil (unclear from source), using 20 subjects.[34,47] No further details provided. 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.[34] No further details were provided.

Sensitization

Human

Salvia Officinalis (Sage) Leaf Extract

The skin sensitization potential of a product containing 0.005% Salvia Officinalis (Sage) Leaf Extract was evaluated in an occlusive human repeated insult patch test (HRIPT) completed in 53 subjects, 25% of whom were reported to have self-perceived sensitive skin; the test article was applied at a 1% dilution in distilled water.[48] Nine, 24-h applications of the test article (0.2. ml; 0.05 ml/cm^3) 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 in the same manner as the induction applications, and reactions were scored at 24 and 72 h after application. Neither irritation nor sensitization occurred during the course of the study. The test material was considered a non-irritant and non-sensitizer.

Salvia Officinalis (Sage) Oil

In a similar manner, an occlusive HRIPT of a body lotion containing 0.03% Salvia Officinalis (Sage) Oil was completed in 53 subjects.[49] Nine, undiluted induction applications of 0.1 – 0.15 g of the test article were made (each for 24 h) over 3-wk. After a 2-wk non-treatment period, a challenge application was made to a previously untreated site and reactions were scored 24 and 72 h after application. No signs of skin reactivity were observed during the induction or challenge phase. The test article was deemed non-irritating and non-sensitizing.

Salvia Officinalis (Sage) Oil or Salvia Officinalis (Sage) Leaf Oil

A maximization test was carried out on 25 subjects.[34] *Salvia officinalis* oil, or *Salvia officinalis* leaf oil, tested at a concentration of 8% in petrolatum did not cause sensitization. No further details provided.

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.[3] 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.[50] 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; further 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.[51] 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 213 formulations, more than half (116) 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 LD_{50} 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 LD_{50} of *Salvia officinalis* oil, or *Salvia officinalis* leaf oil (unclear from source), 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/group died; the acute oral LD_{50} 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 LD_{50} 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 LD_{50} 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 30-d oral dose 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, 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 doses 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, *Salvia officinalis* oil significantly inhibited bacterial growth, however, was not 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 IC_{50} 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 IC_{50} 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 85-yr old woman had positive reactions in a patch test to a lip balm containing *Salvia officinalis* extract, and to 2 of the manufacturer-supplied ingredients, *Salvia officinalis* extract and polygonum, patched separately in water and petrolatum. Patch 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 mainly 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 NOAEL seen in an 8-wk study of rats orally dosed with *Salvia officinalis* oil. Furthermore, the Panel acknowledged the negative human irritation and sensitization data for leaf-derived ingredients, which provided reassurance of the safety of these ingredients because *Salvia officinalis* leaves are the most constituent-rich ingredients, and therefore, would contain the highest levels of potential sensitizers.

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 and Salvia Officinalis (Sage) Extract is used at up to 0.0011% in underarm deodorant spray). Inhalation toxicity data were not available. However, the Panel noted that in aerosol products, 95% – 99% of droplets/ particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial 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 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.

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

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

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

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

TABLES

Table 1: Definitions and functions of *Salvia officinalis* (sage)-derived ingredients[1]

Ingredient/CAS No.	Definition	Function
Salvia Officinalis (Sage) Extract 84082-79-1 (generic)	Salvia Officinalis (Sage) Extract is the extract of the whole plant, *Salvia officinalis*.	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 *Salvia officinalis*.	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 *Salvia officinalis*.	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 *Salvia officinalis*.	Fragrance ingredients
Salvia Officinalis (Sage) Leaf 84082-79-1 (generic)	Salvia Officinalis (Sage) Leaf are the leaves of *Salvia officinalis*.	not reported
Salvia Officinalis (Sage) Leaf Extract 84082-79-1 (generic)	Salvia Officinalis (Sage) Leaf Extract is the extract of the leaves of *Salvia officinalis*.	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 *Salvia officinalis*.	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 *Salvia officinalis*.	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 *Salvia officinalis*.	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, *Salvia officinalis*.	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 *Salvia officinalis*.	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 *Salvia officinalis.*	Fragrance ingredients

Table 2. Chemical properties of *Salvia officinalis* (sage) – derived ingredients

Property	Value	Reference
Salvia Officinalis (Sage) Leaf Extract		
Physical Form	Liquid	[11]
Color	Medium to dark amber	[11]
Refractive Index (@ 25 °C)	1.320 – 1.3450	[11]
Specific Gravity (@ 25 °C)	0.99 – 1.02	[11]
pH (@ 25 °C)	4 – 7	[11]
Solubility	In water	[11]
Salvia Officinalis (Sage) Leaf Water		
Physical Form	Liquid	[14]
Color	colorless	[14]
Density (g/ml @ 20°C)	0.999 – 1.002	[14]
Refractive Index	1.332 – 1.339	[14]
Miscibility	In water and 50% v/v alcohol	[14]
Non-miscibility	Mineral and vegetal oils	[14]
pH	4 – 6.5	[14]
Salvia Officinalis (Sage) Leaf Oil or Oil		
Physical Form	Liquid	[3]
Color	Light yellow to yellow	[3]
Odor	Camphoraceous, herbal, spicy, floral, pine, thujone-like	[52]
Relative Density (@ 20 ºC)	0.9153	[3]
Boiling Point (ºC @ 1013 kPa)	189.3	[3]

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

	Salvia officinalis leaf oil* [24]	Salvia officinalis oil* [13]
Compound	**Percentage (%)**	
cis-salvene	-- (not reported)	0.40
(*Z*)-salvene	0.2	--
(*E*)-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	--
trans-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
p-cymene	0.6	--
limonene	1.5	--
1-napthalenepropanol	--	0.11
1,8-cineole	**26.9**	**22.91**
(*Z*)-β-ocimene	0.1	0.1
γ-terpinene	0.7	0.41
cis-sabinene hydrate	0.1	--
terpinolene	0.2	--
p-cymenene	trace	--
linalool	0.3	--
α- thujone	**17.2**	--
β- thujone	3.8	--
chrysanthenone	trace	--
3-*iso*-thujanol	trace	--
camphor	**12.8**	3.28
neo-iso-3-thujanol	trace	--
trans-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
trans-sabinyl acetate	0.1	--
trans-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	--
aromadendrene	0.4	0.56
myltayl-4 (12)-ene	trace	--
5-oxobornyl acetate	0.1	--
α- humulene	3.1	3.19
9-*epi*-β- caryophyllene	0.1	--
trans-cadina 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	--
carylophylla-4(12),8(13)-dien-5α-ol	0.1	--
manool	0.2	--

Table 4. Frequency (2021)[25] and concentration of use (2020)[26,27] 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*	**66**	**0.000028-0.078**	**1**	**0.0001-0.1**	**213**	**0.000004-0.38**
Duration of Use						
Leave-On	*41*	*0.001-0.078*	*1*	*0.0001*	94	*0.0001-0.38*
Rinse-Off	*25*	*0.000028-0.01*	*NR*	*0.1*	116	*0.000004-0.08*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	3	*0.004*
Exposure Type						
Eye Area	NR	NR	NR	0.0001	4	NR
Incidental Ingestion	3	NR	NR	NR	4	NR
Incidental Inhalation-Spray	15[a]; 17[b]	NR	NR	NR	1; 43[a]; 26[b]	0.0001-0.002; 0.001-0.018[a]
Incidental Inhalation-Powder	17[b]	0.02[c]	NR	NR	26[b]	NR
Dermal Contact	32	0.001-0.078	1	0.0001-0.1	131	0.0002-0.38
Deodorant (underarm)	1[a]	Not spray: 0.001% Spray: 0.0011%	NR	NR	4[a]	NR
Hair - Non-Coloring	30	0.000028-0.003	NR	NR	61	0.000004-0.08
Hair-Coloring	1	NR	NR	NR	17	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	4	0.0035-0.01	NR	NR	36	0.004-0.01
Baby Products	NR	NR	NR	NR	NR	NR
	Salvia Officinalis (Sage) Leaf Oil		**Salvia Officinalis (Sage) Leaf Water**		**Salvia Officinalis (Sage) Oil**	
Totals*	**2**	**0.0028-0.02**	**3**	**0.00071**	**87**	**0.000097-0.22**
Duration of Use						
Leave-On	*NR*	*0.0028-0.02*	2	*0.00071*	56	*0.012-0.22*
Rinse Off	*1*	*0.02*	1	*NR*	25	*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	2	0.005-0.011
Incidental Inhalation-Spray	NR	0.012	1[a]	0.00071[b]	1; 22[a]; 11[b]	0.005[a]
Incidental Inhalation-Powder	NR	NR	NR	0.00071[b]	11[b]	0.22[c]
Dermal Contact	1	0.0028-0.02	3	0.00071	74	0.0097-0.22
Deodorant (underarm)	NR	NR	1[a]	NR	2[a]	NR
Hair - Non-Coloring	NR	NR	NR	NR	11	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
	Salvia Officinalis (Sage) Water					
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 – no reported use

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

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. Genotoxicity studies of *Salvia officinalis* (sage) -derived ingredients

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	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA1537 and *Escherichia coli* WP2uvrA	Bacterial reverse mutation assay	Not genotoxic	[12]
Salvia officinalis oil or *Salvia officinalis* leaf oil	Up to 5000 µg/plate; with and without metabolic activation	Paraffin oil	*S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and *E. coli* WP2	Bacterial reverse mutation assay, in accordance with OECD TG 471.	Not genotoxic	[3]
Salvia officinalis oil	91, 183, or 457 µg, with and without metabolic activation	DMSO	*S. typhimurium* strains TA 98 and TA 100	Ames test	Not genotoxic. Significantly inhibited bacterial growth.	[42]
Salvia officinalis oil	0.25, 0.5, or 1 µl/plate	DMSO	*S. typhimurium* strains TA 98, TA 100, TA 1535, TA1537	Bacterial reverse mutation assay	Not genotoxic	[40]
Salvia officinalis oil	Up to 0.15 mg/ml	Ethanol	*S. typhimurium* strains TA92, TA 94, TA 98, TA 100, TA 1535, TA 1537	Chromosomal aberration test	Not genotoxic	[41]

DMSO- dimethyl sulfoxide

REFERENCES

1. Nikitakis J, Kowcz A. Web-Based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *Dictionary*). http://webdictionary.personalcarecouncil.org/jsp/IngredientSearchPage.jsp. Washington, D.C.: Personal Care Products Council. Last Updated 2022. Accessed 10/21/2021.

2. Karlberg At, Lepoittevin JP. One hundred years of allergic contact dermatitis due to oxidized terpenes: What we can learn from old research on turpentine allergy. *Contact Dermatitis*. 2021.

3. European Chemical Agency (ECHA). REACH registration dossier: Sage, *Salvia officinalis*, ext. (CAS 84082-79-1). https://echa.europa.eu/registration-dossier/-/registered-dossier/25026/1. Last Updated 2018. Accessed 06/30/2020.

4. European Medicines Agency. Assessment report on *Salvia officinalis L.*, *folium* and *Salvia officinalis L.*, *aetheroleum*. 2016. https://www.ema.europa.eu/en/documents/herbal-report/final-assessment-report-salvia-officinalis-l-folium-salvia-officinalis-l-aetheroleum-revision-1_en.pdf. Accessed 06/29/2020.

5. European Medicines Agency. European Union herbal monograph on *Salvia officinalis* L., folium. 2016. https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-monograph-salvia-officinalis-l-folium-revision-1_en.pdf. Accessed 06/29/2020.

6. Jakovljević M, Jokic S, Molnar M, et al. Bioactive profile of various *Salvia officinalis L.* preparations. *Plants (Basel)*. 2019;8(3):55.

7. Ghorbani A, Esmaeilizadeh M. Pharmacological properties of *Salvia officinalis* and its components. *J Tradit Complement Med*. 2017;7(4):433-440.

8. Sharma Y, Fagan J, Schaefer J. Ethnobotany, phytochemistry, cultivation and medicinal properties of Garden sage (*Salvia officinalis L.*). *J Pharmacogn Phytochem*. 2019;8:3139-3148.

9. Solabia. 2009. Specifications data sheet Glycolysat of Sage UP (Salvia Officinalis (Sage) Leaf Extract). Unpublished data submitted by the Personal Care Products Council on April 1, 2021.

10. Martins N, Barros L, Santos-Buelga C, Henriques M, Silva S, Ferreira IC. Evaluation of bioactive properties and phenolic compounds in different extracts prepared from *Salvia officinalis L*. *Food Chem*. 2015;170:378-385.

11. Anonymous. 2020. Salvia Officinalis (Sage) Leaf Extract (method of manufacture, impurities and specifications). Unpublished data submitted by Personal Care Products Council on December 10, 2020.

12. Anonymous. 2021. Summary Information Salvia Officinalis (Sage) Leaf Extract. Unpublished data submitted by Personal Care Products Council on January 5, 2021.

13. Mehdizadeh T, Hashemzadeh M, Nazarizadeh A, et al. Chemical composition and antibacterial properties of *Ocimum basilicum*, *Salvia officinalis* and *Trachyspermum ammi* essential oils alone and in combination with nisin. *Res J Pharmacogn*. 2016;3(4):51-58.

14. Solabia. 2009. Specifications data sheet Vegebios of Sage 1.5P (Salvia Officinalis (Sage) Leaf Water). Unpublished data submitted by the Personal Care Products Council on April, 2021.

15. Stojanovic D, Lakušić B, Ristić M, Slavkovska V, Lakusic D. Variations in essential oil yields and compositions of *Salvia officinalis* (*Lamiaceae*) at different developmental stages. *Bot Serb*. 2013;37:127-139.

16. Walch SG, Tinzoh LN, Zimmermann BF, Stühlinger W, Lachenmeier DW. Antioxidant capacity and polyphenolic composition as quality indicators for aqueous infusions of *Salvia officinalis L.* (sage tea). *Front Pharmacol*. 2011;2:79.

17. Tober C, Schoop R. Modulation of neurological pathways by *Salvia officinalis* and its dependence on manufacturing process and plant parts used. *BMC Complement Altern Med*. 2019;19(1):128.

18. Baranauskiene R, Dambrauskienė E, Venskutonis R, Viskelis P. 2011. Influence of harvesting time on the yield and chemical composition of sage (*Salvia officinalis L.*). Conference proceedings presented at FoodBalt, May 5-6, 2011.

19. Arraiza M, Arrabal C, López JV. Seasonal Variation of Essential Oil Yield and Composition of Sage (*Salvia officinalis L.*) Grown in Castilla - La Mancha (Central Spain). *Notulae Botanicae Horti Agrobotanici Cluj-Napoca*. 2012;40:106-108.

20. Brancato A, Brocca D, Lentdecker C, et al. Modification of the existing maximum residue levels for ametoctradin in herbs and edible flowers. *EFSA J*. 2017;15(9).

21. European Food Safety Authority (EFSA). Reasoned opinion on the modification of the existing MRLs for ametoctradin in sage and basil. *EFSA J*. 2015;13(6):4153.

22. Szpyrka E, Słowik-Borowiec M. Consumer health risk to pesticide residues in *Salvia officinalis L.* and its infusions. *J Environ Sci Health B*. 2019;54(1):14-19.

23. Afonso AF, Pereira OR, Fernandes Â, et al. Phytochemical composition and bioactive effects of *Salvia africana*, *Salvia officinalis* 'Icterina' and *Salvia mexicana* aqueous extracts. *Molecules* 2019;24(23):4327.

24. Craft JD, Satyal P, Setzer WN. The Chemotaxonomy of common sage (*Salvia officinalis*) based on the volatile constituents. *Medicines (Basel)*. 2017;4(3):47.

25. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2021; received January 21, 2021.

26. Personal Care Products Council. 2020. Concentration of Use by FDA Product Category: Sage-Derived Ingredients. Unpublished data submitted by Personal Care Products Council on February 26, 2020.

27. Personal Care Products Council. 2020. Concentration of Use by FDA Product Category: Salvia Officinalis (Sage) Leaf Oil. Unpublished data submitted by Personal Care Products Council on October 27, 2020.

28. Johnsen MA. The Influence of Particle Size. *Spray Technology and Marketing*. 2004;14(11):24-27.

29. Rothe H. 2011 2011. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. Unpublished data presented at the 26 September Expert Panel meeting. Washington D.C.

30. 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. Bilthoven, Netherlands: Netherlands National Institute for Public Health and the Environment; 2006. RIVM 320104001/2006. Pages 1-77. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Accessed 8/24/2011.

31. 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.

32. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009 https://ec.europa.eu/health/sites/health/files/endocrine_disruptors/docs/cosmetic_1223_2009_regulation_en.pdf. Last Updated 2020. Accessed 04/14/2020.

33. International Fragrance Association (IFRA). IFRA Standard 49th Amendment: Thujone. https://ifrafragrance.org/standards/IFRA_STD_102.pdf. Last Updated 01/10/2020. Accessed 07/14/2020.

34. Research Institute for Fragrance Materials (RIFM). Sage Oil, Dalmatian. In: Opdyke DLJ, ed. *Monographs on Fragrance Raw Materials: A Collection of Monographs Originally Appearing in Food and Cosmetics Toxicology*. . Pergamon Press; 1979: 672.

35. Grdiša M, Jug-Dujaković M, Lončarić M, et al. Dalmatian Sage (*Salvia officinalis L.*): A review of biochemical contents, medical properties and genetic diversity. *Agric Conspec Sci*. 2015;80(2):69-78.

36. Rodrigues MRA, Kanazawa LKS, das Neves TLM, et al. Antinociceptive and anti-inflammatory potential of extract and isolated compounds from the leaves of *Salvia officinalis* in mice. *J Ethnopharmacol*. 2012;139(2):519-526.

37. Sabry MM, Abdel-Rahman RF, El-Shenawy SM, Hassan AM, El-Gayed SH. Estrogenic activity of Sage (*Salvia officinalis L.*) aerial parts and its isolated ferulic acid in immature ovariectomized female rats. *J Ethnopharmacol*. 2022;282:114579.

38. Monsefi M, Abedian M, Azarbahram Z, Ashraf MJ. *Salvia officinalis L.* induces alveolar bud growing in adult female rat mammary glands. *Avicenna J Phytomed*. 2015;5(6):560-567.

39. Domaracký M, Rehák P, Juhás Š, Koppel J. Effects of selected plant essential oils on the growth and development of mouse preimplantation embryos in vivo. *Physiol Res*. 2007;56(1):97-104.

40. Zani F, Massimo G, Benvenuti S, et al. Studies on the genotoxic properties of essential oils with *Bacillus subtilis* rec-assay and *Salmonella*/microsome reversion assay. *Planta Med*. 1991;57(3):237-241.

41. Ishidate M, Jr., Sofuni T, Yoshikawa K, et al. Primary mutagenicity screening of food additives currently used in Japan. *Food Chem Toxicol*. 1984;22(8):623-636.

42. De Martino L, De Feo V, Nazzaro F. Chemical composition and in vitro antimicrobial and mutagenic activities of seven *Lamiaceae* essential oils. *Molecules*. 2009;14(10):4213-4230.

43. Vujosevic M, Blagojević J. Antimutagenic effects of extracts from sage *(Salvia officinalis*) in mammalian system in vivo. *Acta Vet Hung*. 2004;52(4):439-443.

44. Zare H. Effects of *Salvia officinalis* extract on the breast cancer cell line. *Sci Med Journ*. 2019;1(1):25-29.

45. Río ÁGd, Sanz J, Coloma AG, et al. Cytotoxic activity of ±-humulene and transcaryo- phyllene from *Salvia officinalis* in animal and human tumor cells. *An R Acad Nac Farm*. 2010;76(3):343-356.

46. Loizzo M, Tundis R, Menichini F, Saab A, Statti G, Menichini F. Cytotoxic activity of essential oils from *Labiatae* and *Lauraceae* families against in vitro human tumor models. *Anticancer Res*. 2007;27(5A):3293-3299.

47. Tisserand R, Young R. *Essential Oil Safety: A Guide for Health Care Professionals.* 2nd ed. Edinburgh, United Kingdom: Churchill Livingston, Elsevier; 2014.

48. Anonymous. 2017. Clinical safety evaluation repeated insult patch test (product contains 0.005% Salvia Officinalis (Sage) Leaf Extract (1% dilution tested)). Unpublished data submitted by the Personal Care Products Council on April 29, 2021.

49. Anonymous. 2000. Repeated insult patch test (body lotion containing 0.03% Salvia Officinalis (Sage) Oil. Unpublished data submitted by the Personal Care Products Council on April 29, 2021.

50. Mayer E, Gescheidt-Shoshany H, Weltfriend S. Allergic contact dermatitis caused by *Salvia officinalis* extract. *Contact Dermatitis*. 2011;64(4):237-238.

51. Selvaag E, Holm JO, Thune P. Allergic contact dermatitis in an aroma therapist with multiple sensitizations to essential oils. *Contact Dermatitis*. 1995;33(5):354-355.

52. Jirovetz L, Buchbauer G, Denkova Z, Slavchev A, Stoyanova A, Schmidt E. Chemical composition, antimicrobial activities and odor descriptions of various *Salvia sp*. and *Thuja sp.* essential oils. *Nutrition-Vienna-*. 2006;30(4):152.