GREEN

Safety Assessment of Rosmarinus Officinalis (Rosemary)-Derived Ingredients as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	August 16, 2013
Panel Meeting Date:	September 9-10, 2013

The 2013 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Monice M. Fiume, Senior Scientific Analyst/Writer.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume *MMF*
Senior Scientific Analyst/Writer
Date: August 16, 2013
Subject: Safety Assessment of Rosmarinus Officinalis (Rosemary)-Derived Ingredients as Used in Cosmetics

Enclosed is the Draft Report on the Safety Assessment of Rosmarinus Officinalis (Rosemary)-Derived Ingredients as Used in Cosmetics. This is the first time the Panel is seeing this document on these 12 ingredients. The Scientific Literature Review was issued on June 7, 2013.

Comments on the SLR that were received from the Personal Care Products Council mostly have been addressed. (You will find a copy of all the comments included with this submission.) One comment – the first Key Issue listed by the Council - does need your particular attention, however. The Council asked for an explanation as to why Rosmarinic Acid is included as an ingredient in this report, while other constituents that are also cosmetic ingredients, are not.

There is a precedent of CIR including the acid of a botanical in the family of ingredients; as a result, Rosmarinic Acid was included in this safety assessment. However, your input on this matter would be greatly appreciated.

So that you have as complete a picture as possible, information on the chemical composition of *Rosmarinus officinalis* is provided in Tables 3-6. Table 7 provides information on the toxicity of some of the constituents.

The following data submissions were received from the Council and are included with this report:

1. Rosmarinus officinalis (rosemary) leaf extract: composition information; dated April 22.
    a. Natural Sourcing. 2013. Organic rosemary oil extract;
    b. Natural Sourcing. 2013. Rosemary antioxidant extract – 14% diterpene phenols;
    c. Natural Sourcing. 2013. Rosemary antioxidant extract – 25% diterpene phenols;
    d. Natural Sourcing. 2011. CO_2 rosemary extract select certificate of analysis;
    e. Natural Sourcing. 2012. Organic rosemary antioxidant CO_2 extract 14% diterpene phenols certificate of analysis;
    f. Natural Sourcing. 2013. Organic rosemary antioxidant CO_2 extract 25% diterpene phenols certificate of analysis;
    g. Natural Sourcing. 2012. Rosemary essential oil certificate of analysis.
2. Rosmarinus officinalis (rosemary) leaf extract; dated May 31.
    a. Flavex Naturextrakte GmbH. 2010. Rosemary antioxidant CO_2 extract 25% diterpene phenols, type no. 027.020 25% diterpene phenols;
    b. Flavex Naturextrakte GmbH. 2013. Certificate of analysis: Rosemary antioxidant extract 25% diterpene phenols, type no. 027.020;

c. Flavex Naturextrakte GmbH. 2013. Allergen compounds according to Cosmetic Guideline 76/768/EEC Rosemary antioxidant extract 25% diterpene phenols, type no. 027.020;
d. Official Journal of the European Union. 2010. Commission Directive 2010/69/EU of 22 October 2010 amending the Annexes to the European Parliament and Council Directive 95/2/EC on food additives other than colours and sweeteners.

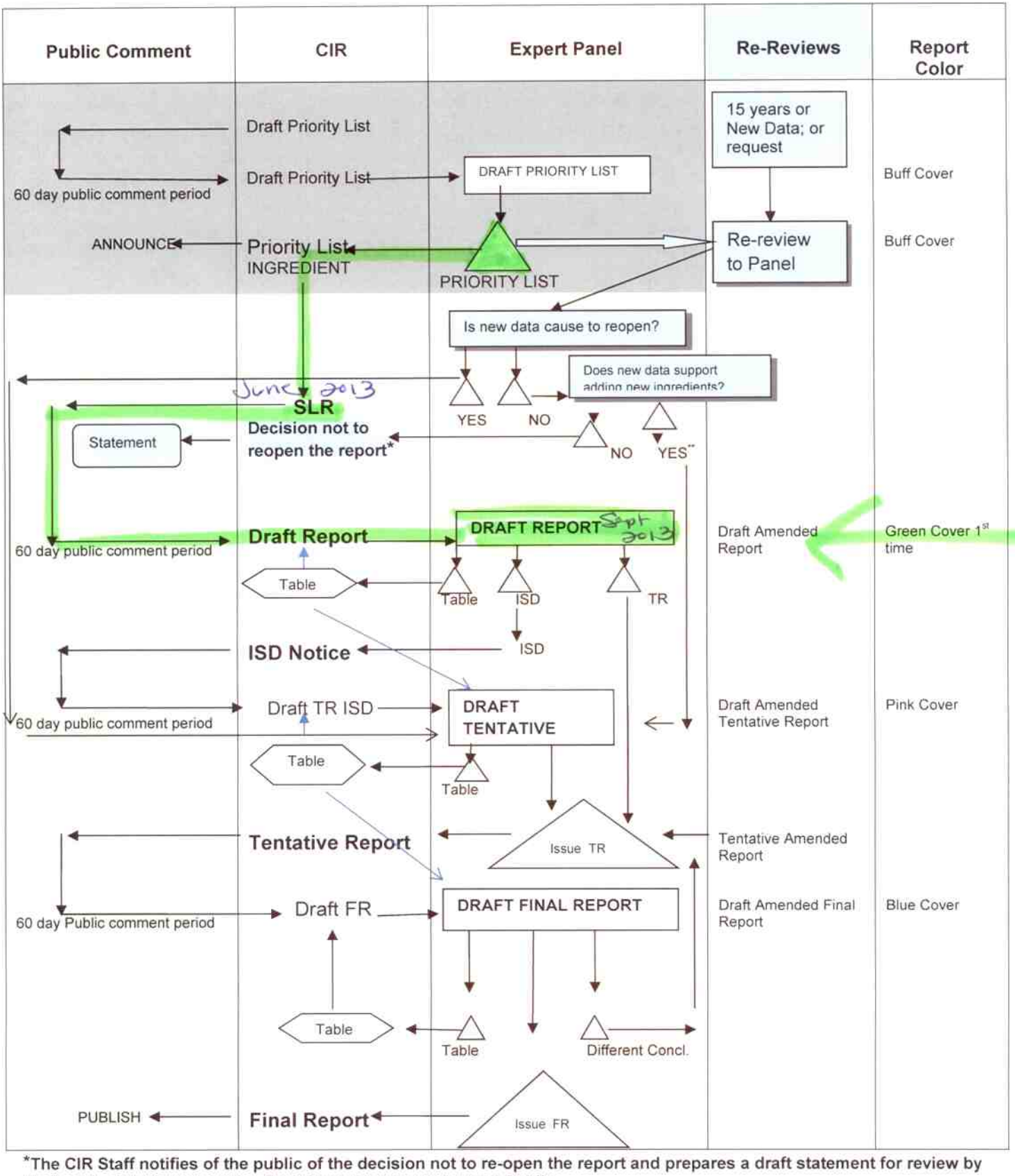
3. Updated concentration of use by FDA product category: Rosemary-derived ingredients (added rosemary leaf oil). Memo dated June 14, 2013.
4. Concentration of use by FDA product category: Rosmarinic acid. Memo dated July 29, 2013.

After reviewing this document, if you find that the current data adequately address the safety of the Rosmarinus officinalis (rosemary)-derived ingredients, the Panel should be prepared to formulate a tentative conclusion, provide the rationale to be described in the Discussion, and issue a Tentative Report for public comment. If the data are not sufficient for making a determination of safety, then an Insufficient Data Announcement should be issued that provides a listing of the additional data that are needed.

Rosmarinus Officinalis (Rosemary) Ingredients

SAFETY ASSESSMENT FLOW CHART

Sept 2013



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

△ Expert Panel Decision

Rosmarinus Officinalis (Rosemary)-Derived Igngredients Report History

June 7, 2013: Scientific Literature Review

The following data submissions were received from the Council:

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September 9-10, 2013: Draft Report for Panel Consideration

Rosmarinus Officinalis (Rosemary)-Derived Ingredients Data Profile* – Sept 2013 – Monice Fiume

	Reported Use	Preparation/ Extraction	Constituents/ Impurities	Toxicokinetics	Animal Tox – Acute, Derrmal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhalation	Animal Tox – Rptd Dose, Dermal	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhalaiton	Repro/Dev Tox	Genotox	Carcinogenicity/ Anti-Tumor Act	Dermal Irr/Sens	Ocular Irritation
Rosmarinus officinalis L.			X												
Rosmarinus Officinalis (Rosemary) Extract	X														
Rosmarinus Officinalis (Rosemary) Flower Extract	X		X												
Rosmarinus Officinalis (Rosemary) Flower/Leaf Stem Extract	X										X				
Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Water															
Rosmarinus Officinalis (Rosemary) Flower Wax															
Rosmarinus Officinalis (Rosemary) Leaf	X					X						X			
Rosmarinus Officinalis (Rosemary)Leaf Extract	X	X				X			X		X	X	X	X	
Rosmarinus Officinalis (Rosemary) Leaf Oil	X	X			X	X			X			X		X	
Rosmarinus Officinalis (Rosemary) Leaf Powder	X														
Rosmarinus Officinalis (Rosemary)Leaf Water	X														
Rosmarinus Officinalis (Rosemary) Water	X														
Rosmarinic Acid		X		X					X			X	X	X	

*"X" indicates that data were available in a category for the ingredient

Rosmarinus Officinalis (Rosemary)-Derived Ingredients

Keep Me Posted Results are obtained weekly

SciFinder Substance Search (Feb 12, 2013)

84604-14-8
8000-25-7
Rosmarinus Officinalis (Rosemary) Extract
Rosmarinus Officinalis (Rosemary) Flower Extract
Rosmarinus Officinalis Flower/Leaf Stem Extract
Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Water
Rosmarinus Officinalis (Rosemary) Flower Wax
Rosmarinus Officinalis (Rosemary) Leaf
Rosmarinus Officinalis (Rosemary) Leaf Extract
Rosmarinus Officinalis (Rosemary) Leaf Oil
Rosmarinus Officinalis (Rosemary) Leaf Powder
Rosmarinus Officinalis (Rosemary) Leaf Water
Rosmarinus Officinalis (Rosemary) Water

- 2 substances found – via above CAS No.
    - 84604-14-8 – 0 hits
    - 8000-25-7 – 49 hits/7 selected for further examination

Searched
- effects of rosemary on reproduction or fertility?
    - 178 hits; 1 selected for further examination
- Estrogenic effects of rosemary
    - 14 hits; 3 selected for further examination
- Dermal irritation and sensitization and rosemary
    - 73 hits; 3 selected for further examination

Added Rosmarinic Acid/searched Mar 7, 2013: 20283-92-5; pulled 4 hits from SciFinder – because also searched PubMed

PubMed Search (Feb 12, 2013)
(rosmarinus AND officinalis) OR rosemary – 1291 hits/44 selected for further examination

"20283-92-5" OR (rosmarinic AND acid) OR (rosemary AND acid) – (Mar 8, 2013) – 935 hits/19 selected for further examination

ChemPortal
nothing useful

IARC
Found info on constituents

NTP
Found info on constituents

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INTRODUCTION

This report reviews the safety of the following 12 Rosmarinus officinalis (rosemary)-derived ingredients as used in cosmetic formulations:

Rosmarinus Officinalis (Rosemary) Extract
Rosmarinus Officinalis (Rosemary) Flower Extract
Rosmarinus Officinalis (Rosemary) Flower/Leaf Stem Extract
Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Water
Rosmarinus Officinalis (Rosemary) Flower Wax
Rosmarinus Officinalis (Rosemary) Leaf
Rosmarinus Officinalis (Rosemary) Leaf Extract
Rosmarinus Officinalis (Rosemary) Leaf Oil
Rosmarinus Officinalis (Rosemary) Leaf Powder
Rosmarinus Officinalis (Rosemary) Leaf Water
Rosmarinus Officinalis (Rosemary) Water
Rosmarinic Acid

Most of the ingredients included in this review are extracts, oils, powders, solutions, or waxes derived from a defined part of the Rosmarinus officinalis (rosemary) plant. Rosmarinic acid is an acid that can be obtained from *Rosmarinus officinalis*; therefore it also is being included in this safety assessment.

While Rosmarinus officinalis (rosemary)-derived ingredients are reported to have a number of functions, the most common functions in cosmetics are use as a skin conditioning agent or use as a fragrance ingredient.[1] Three of the ingredients, i.e., Rosmarinus officinalis (rosemary) flower extract, Rosmarinus officinalis (rosemary) leaf extract, and rosmarinic acid, are reported to function as antioxidants. Rosmarinus officinalis (rosemary) leaf powder is reported to function only as a flavoring agent.

CHEMISTRY

Definition

The definition and chemical class of each Rosmarinus officinalis (rosemary)-derived ingredient included in this report are provided in Table 1. The definition indicates what part(s) of the plant the ingredient is obtained from. In some cases, the definition also gives insight as to the method of manufacture.

Rosmarinic acid, a constituent of the plant, is an ester of caffeic acid and 3,4-dihydrophenyllactic acid.[2] The structure is depicted in Table 1.

General Characterization

The *Rosmarinus officinalis* L. plant, from the botanical family Lamiaceae, is a scented, evergreen shrub with a very pungent odor that is native to the Mediterranean region and Portugal; the odor is sometimes defined as camphor-like. It has a spicy, harsh, bitter, aromatic taste.[3-5] Bluish labiate flowers grow on the upper green part of the branches.[3-5] The oil is produced mostly in Spain, France, and Tunisia.[6]

Rosmarinus officinalis L. is generally recognized as safe (GRAS) as a spice and other natural seasoning and flavoring (21CFR182.10) Rosemary has traditional or folk medicine uses, some with reported side effects.[3,4,7] The leaves are considered the medicinal part of the plant in herbal medicine.[4]

Rosmarinic acid is present in many plants; it occurs throughout the Boraginaceae family, but in the Lamiaceae family it is restricted to the Nepetoideae sub-family.[2] It occurs in *Rosmarinus officinalis*, *Melissa officinalis*, *Ocimum basilisum*, *Perilla frutescens*, *Artemisia capillaris*, *Calendula officinalis* L., and *Saliva officinalis*, and in ferns of the Blechnaceae family.[2,8-10]

Chemical and Physical Properties

Rosmarinus officinalis (rosemary)-derived ingredients are strongly aromatic. The chemical and physical property data that were available are provided in Table 2.

Preparation/Extraction

Rosmarinus Officinalis (Rosemary) Leaf Extract

Food-grade Rosmarinus officinalis (rosemary) extract is prepared by extraction from the leaves of *Rosmarinus officinalis*. Food-grade acetone, ethanol, hexane, or a combination of hexane and ethanol (in a two-step process) are used as extraction solvents; the extract can also be prepared from a deodorized or partially deodorized ethanol extract of rosemary.[11,12] Food-grade Rosmarinus officinalis (rosemary) extract may also be extracted using supercritical carbon dioxide (CO_2). Subsequent production steps include filtration, purification, solvent evaporation, drying, and sieving. The extract may be deodorized, decolorized, and standardized using diluents and carriers that are permitted in foods.

Supplier-provided data sheets report production of Rosmarinus officinalis (rosemary) leaf extracts by supercritical fluid extraction with natural CO_2 and a small amount of ethanol as a solvent.[13-15] One supplier reported that the essential oil is removed by multistep separation.[15]

Additional methods include extraction with absolute ethanol (resulting in what has been called “an absolute”) or a collection of the insoluble waxes (resulting in what has been called “a concrete”).[16]

Rosmarinus Officinalis (Rosemary) Leaf Oil

Food-grade Rosmarinus officinalis (rosemary) leaf oil is the volatile oil obtained by steam distillation from the fresh flowering tops or dried crushed aerial parts of *Rosmarinus officinalis* L.[17] The oil from *Rosmarinus officinalis* is also obtained by hydrodistillation of dried crushed aerial parts.[18]

One supplier reported their Rosmarinus officinalis (rosemary) leaf oil is produced by supercritical fluid extraction with natural CO_2 and a small amount of ethanol.[19] This supplier adds a small amount (<4%) of sunflower oil to increase solubility when blending.

Rosmarinic Acid

Relatively large-scale production of rosmarinic acid can be obtained from a cell culture of *Coleus blumei* Benth. by supplying exogenous phenylalanine and tyrosine.[7]

Rosmarinic acid is extracted from *Rosmarinus officinalis* leaves using hot water; the extract is filtered while hot and then mixed with an alcohol mixture.[20] Ursolic acid, isolated from a separate process and then purified, is added to the extract.

Constituents/Impurities

Rosmarinus officinalis L. is composed of an array of constituents, primarily phenolic acids, flavonoids, monoterpenes, diterpenes, diterpenoids, triterpenes, and rosmarinic acid. Structures for some of the principal components according to chemical family are depicted in Figures 1-5.

A detailed list of chemical constituents by plant part is presented in Table 3, and a more focused listing of constituents of *Rosmarinus officinalis* is provided in Table 4. Table 5 provides composition data on three Rosmarinus officinalis (rosemary) leaf extracts, based on certificates of analysis provided by suppliers of Rosmarinus officinalis (rosemary) leaf extract; these certificates were provided by suppliers and report a phenolic diterpenes content of 14 or 25%.[21-24]

According to Cosmetic Guideline 76/768/EEC, specific allergen compounds are subject to declaration on the label if the concentration of this substance exceeds 0.001% in leave-on and 0.01% in rinse-offs. One supplier reported, separately from the certificate of analysis, the following concentrations of allergen compounds in a Rosmarinus officinalis (rosemary) leaf extract that needed to be declared: <0.1% linalool and <0.2% d-limonene.[25]

The principal antioxidative components of Rosmarinus officinalis (rosemary) leaf extract are the phenolic diterpenes carnosol and carnosic acid.[12] The amount of carnosol and carnosic acid present in the extract varies with the method of extraction, with levels as low as 5-7% carnosol plus carnosic acid found in rosemary extract prepared from a partially deodorized ethanol extract of rosemary to as high as 30% carnosol plus carnosic acid in an extract prepared with supercritical carbon dioxide.[3,11]

According to the *Food Chemicals Codex*, food-grade Rosmarinus officinalis (rosemary) leaf extract is characterized by the content of carnosic acid and carnosol; using high-performance liquid chromatography, suitability requirement 1 states the tailing factor for the carnosic acid peak response is not more than 0.90-1.30, and suitability requirement 2 states the relative standard deviation for the carnosic acid peak response is not more than 2%.[11]

Carnosol and carnosic acid are not the only constituents that vary with extraction method. Table 6 provides a sample of the differences in constituent profiles in rosemary leaves based on extraction method. Some of the studies summarized in this report provided information on the amount of constituents present in the test article; when this information was available, it is included.

In addition to extraction method, the actual amount of constituents present also varies according to the stage of development, variety of plant, season harvested, and origin of the leaves.[3,12,26,27] Water and light conditions also affect the amount of the constituents found in rosemary plants; for example, highly oxidized diterpenes increase in rosemary plants exposed to drought and high light stress.[28] Although it is generally accepted that the geographical region and stage of growth affects plant composition, some researchers reported that, within one country, the chemical composition of rosemary essential oil (plant parts not specified) did not vary with geographical region or harvest time.[29]

Food-grade Rosmarinus officinalis (rosemary) leaf extract has acceptance criteria of not more than 3 mg/kg arsenic and 2 mg/kg lead, and not more than 8.0% loss on drying.[11] Food-grade rosemary leaf oil is to have not less than 8.0% borneol and not less than 1.5% esters, calculated as bornyl acetate.[17]

Table 7 provides toxicity and other information on some constituents of Rosmarinus officinalis (rosemary)-derived ingredients.

USE

Cosmetic

The Rosmarinus officinalis (rosemary)-derived ingredients included in this safety assessment have a variety of functions in cosmetics. However, most of the ingredients function as a skin conditioning agent and/or as a fragrance ingredient; Rosmari-

nus officinalis (rosemary) leaf powder is reported to function only as a flavoring agent.[1] A listing of all the reported functions for each ingredient is provided in Table 1.

The Food and Drug Administration (FDA) collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). VCRP data obtained from the FDA[30] and data received in response to a survey of the maximum reported use concentration by category conducted by the Personal Care Products Council (Council)[31,32] in 2013 indicate that nine of the twelve ingredients included in this safety assessment are used in cosmetic formulations. Rosmarinus officinalis (rosemary) leaf extract has the greatest number of uses, 689, followed by Rosmarinus officinalis (rosemary) leaf oil, 516. According to the results of the concentration of use survey, most cosmetic formulations contain very low concentrations of the Rosmarinus officinalis (rosemary)-derived ingredients, often much less than 0.1%. However, Rosmarinus officinalis (rosemary) leaf extract is reported to be used at up to 10% in body and hand products and 3% in eye shadow formulations and bath soaps and detergents. Three ingredients are not reported to be used: Rosmarinus officinalis (rosemary) flower/leaf/stem water; Rosmarinus officinalis (rosemary) flower wax; and rosmarinic acid.

Frequency and concentration of use data categorized by exposure and duration of use are provided in Table 8. In some cases, reports of uses were received in the VCRP, but no concentration of use data are available. For example, Rosmarinus officinalis (rosemary) flower extract is reported to be used in 36 cosmetic formulations, but no use concentration data were reported. Additionally, for Rosmarinus officinalis (rosemary) flower/leaf/stem extract, no reported uses were received in the VCRP, but a use concentration was provided in the industry survey; it should be presumed there is at least one use in a deodorant formulation, the category for which the concentration of use was reported.

Products containing Rosmarinus officinalis (rosemary)-derived ingredients may be applied to baby skin (e.g., 0.012% Rosmarinus officinalis (rosemary) leaf extract in baby lotion, oils and creams), used in products that could be incidentally ingested (e.g., 0.012% Rosmarinus officinalis (rosemary) leaf in lipstick formulations), or used near the eye area or mucous membranes (e.g., up to 3% Rosmarinus officinalis (rosemary) leaf extract in eye shadow formulations and in bath soaps and detergents).[31] Additionally, Rosmarinus officinalis (rosemary)-derived ingredients are used in cosmetic sprays and powders; for example, Rosmarinus officinalis (rosemary) leaf extract is used in other fragrance preparations at up to 0.5% and Rosmarinus officinalis (rosemary) extract is used in face powders at up to 0.05%. These products could possibly be inhaled. In practice, 95 to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm.[33-36] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[33,36] Rosmarinus officinalis (rosemary) leaf extract is used in aerosol deodorants at concentrations up to 0.012%. 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.[33] 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 Rosmarinus officinalis (rosemary) ingredients named in this safety assessment are listed in the European Union inventory of cosmetic ingredients.[37]

Non-Cosmetic

Rosmarinus officinalis L. is GRAS as a spice and other natural seasoning and flavoring when the intended use is for human consumption (21CFR182.10) and for animal drugs, feed, and related products (21CFR582.10). It is also GRAS as an essential oil, oleoresin (solvent-free), and natural extractive (including distillates) for human consumption (21CFR182.20) and for animal drugs, feed, and related products (21CFR582.20). Rosemary oil can be used in the formulation of denatured alcohol and rum (27CFR21.65).

In *The Official Journal of the European Union*, extracts of rosemary contain several anti-oxidant compounds, and although the European Food Safety Authority (EFSA) was not able to establish an acceptable daily intake due to insufficient toxicological data, the EFSA considered the margin of safety was high enough to conclude that dietary exposure was not a concern.[38] Extracts of rosemary are allowed in various food products at amounts of 30-1000 mg/kg, expressed as the sum of carnosol and carnosic acid.

Rosemary leaves are used as a seasoning in cooking.[39] Rosmarinus officinalis (rosemary) leaf oil is used as a condiment and flavoring agent in food; as an antioxidant in edible oils, meats, and other fat-containing foods; and as a dietary supplement. Rosemary oil is reported to have antimicrobial activities.[6]

Rosemary is reported to have use as an anti-inflammatory, antioxidant, and anti-microbial agent.[2,20,26,40] Rosemary has traditional or folk medicine uses, some with reported side effects.[3,4,7] It has been used as an antispasmodic in renal colic and dysmenorrhea, and it has been used for relieving respiratory disorders. The essential oil is used internally as a carminative and as an appetite stimulant; however, large amount of the oil are reported to cause gastroenteritis and nephritis. The *PDR for Herbal Medicines* states that one is advised against using rosemary during pregnancy due to toxic side effects from components of the oil. The essential oil is added to bath water as a circulation stimulant. As the oil or as an ointment, external

application use is as an analgesic liniment for rheumatism. Rosemary is used as a poultice for poorly healing wounds and in the treatment of eczema. It is used in lotions to treat baldness,[18] and the leaves and branches have been used for treating headaches.[6]

TOXICOKINETICS

Absorption, Distribution, Metabolism, Excretion

Dermal

Rosmarinic Acid

Rosmarinic acid had good permeability through rat skin *in vitro*, with higher permeation occurring from an ethanol solution than an aqueous solution. The transdermal permeation of 3.921 mg/ml [^{3}H]rosmarinic acid was determined *in vitro* using full thickness dorsal rat skin.[41] A volume of 250 µl of the test solution was applied to the stratum corneum of a 15 mm diameter skin sample, and the sample was covered with paraffin film to prevent evaporation. Distilled water (n=4) and 95% ethanol (n=5) were used as the test solvents. Receptor phase samplings were taken at various times between 0.5 and 96 h after application. With water as the solvent, steady state permeation across rat skin was maintained from 17-72 h after application of rosmarinic acid to the skin sample. With the ethanol solvent, steady state permeation was maintained from 6-26 h. Permeation plateaued after that time. The flux of rosmarinic acid was greater from the ethanol solution than from water; flux was 4.4 ± 1.3 µg·cm^2/h with water and 10 ± 6 µg·cm^2/h with ethanol. The permeability of rosmarinic acid was calculated using three methods: as the ratio of the product of flux and stratum corneum thickness, for which permeability was calculated as 4.9×10^{-5} cm^2/h with water and 3.8×10^{-6} cm^2/h with ethanol; as the product of flux and full skin thickness, for which permeability was calculated as 5.7×10^{-5} cm^2/h with water and 4.4×10^{-4} cm^2/h with ethanol; and as the ratio of flux to initial concentration, for which permeability was calculated as 3.2×10^{-4} cm/h with water and 2.6×10^{-3} cm/h with ethanol.

The distribution of rosmarinic acid was determined in rat skin.[41] Skin discs, 8.5 mm in diameter, were taken from six rats; the discs were approximately 1.7 mm in thickness and 20 µm slices were cut using a microtome. The test solution was 3.921 mg/ml [^{3}H]rosmarinic acid in 95% hydro-alcoholic solvent, and the study was terminated at 24 h for steady state permeation, and at 118 h, at which time the permeation had plateaued. At steady state, the concentration found in the upper layers of the skin (≤200 µm) were 16-fold higher than in the lower skin layers (1000-1700 µm); the concentration of rosmarinic acid was 1600 µg/ml tissue at a skin depth of 200 µm, as opposed to approximately 100 µg/ml at a skin depth of 1700 µm. In skin samples evaluated after 118 h, minimal rosmarinic acid was found in the skin. At a skin depth of 100 µm, the concentration of rosmarinic acid was approximately 100 µg/ml tissue.

A total of 7.843 mg of [^{3}H]rosmarinic acid in 500 mg of a w/o emulsion ointment was applied to a 5 cm x 10 cm area on the dorsal skin of six male Sprague-Dawley rats, providing a dose of 26.21 mg/kg.[41] The test site was enclosed by skin cement and covered with aluminum foil and an adhesive bandage. Blood samples were taken at various intervals for 12 h, and concentration-time profiles were analyzed by a compartment model independent technique. Blood concentration-time data showed two peaks, one at 1 h, and the other at 4.5 h. The researchers hypothesized there could be three possibilities for the double peak: (1) rosmarinic acid may undergo biliary recycling; (2) it may be well-absorbed initially, resulting in the first peak, and then because of the occlusion effect caused by the aluminum foil, with reverse direction of water stream in the skin, the second peak occurs; and/or (3) after time the emulsion breaks or reverses, enhancing further absorption. Total body clearance was 101.25 ml/min/kg. The absolute bioavailability, calculated using both intravenous (i.v.; study described later) and topical areas under the curve (AUC) corrected for dose and body wt, was 60%, indicating substantial transdermal systemic absorption.

The researchers also evaluated the tissue distribution of [^{3}H]rosmarinic acid in rats.[41] An application of 3.137 mg rosmarinic acid in 200 mg ointment base, providing a dose of 9.45 mg/kg, was applied to the leg of each of three male Sprague-Dawley rats. The area of application was 19.6 cm^2. The legs were immobilized, the sites were covered as described previously, and the rats were killed after 4.5 h. The amount of unabsorbed rosmarinic acid was recovered from the skin and the aluminum foil was 45%, indicating that 55% was taken up by the skin. The highest concentration of rosmarinic acid was found in the skin, 19.04 µg/g. Rosmarinic acid was also found in the muscle (1.61 µg/g) and bone (0.047 µg/g); values were not determined in the blood, brain, heart, liver, lung, or spleen.

Oral

Rosmarinic Acid

Five male Sprague-Dawley rats were dosed by gavage with 200 mg/kg rosmarinic acid as a 20% ethanol solution.[42] (The rosmarinic acid was isolated from a product made from *Perilla frutescens*.) Urine was collected for 72 h. Bile and blood samples were collected at 12 h after dosing. The following seven metabolites were isolated in the urine (with cumulative mean % of dose in 0-72 h given in parentheses):

1.) *trans*-caffeic acid-4-*O*-sulfate (0.154%);
2.) *trans*-*m*-coumaric acid-3-*O*-sulfate (12.14%);
3.) *trans*-ferulic acid-4-*O*-sulfate (0.58%);

4.) *trans*-caffeic acid (0.12%);
5.) *m*-hydroxyphenylpropionic acid (18.36%);
6.) *trans-m*-coumaric acid (0.41%); and
7.) unchanged rosmarinic acid (0.08%).

The total cumulative amount excreted in the urine was 31.8% of the dose. None was found in the bile.

The absorption and metabolism of 50 mg/kg bw aq. rosmarinic acid was determined in five fasted Sprague-Dawley rats; rosmarinic acid was rapidly absorbed from the gastrointestinal tract, and it was metabolized into conjugated and/or methylated forms.[43] The animals were dosed by gavage with 5 mg/ml rosmarinic acid; five control animals were given 10 ml/kg bw distilled water. Blood was collected at various intervals for up to 18 h after dosing, and urine samples were collected at 0-8 and 8-18 h after dosing. In plasma, total rosmarinic acid compounds (free and conjugate forms) reached a maximum concentration of 4.3 µmol/l at 30 min after dosing. A maximum concentration of total methyl-rosmarinic acid (5.03 µmol/l) occurred after 1 h, and the maximum *m*-coumaric acid concentration (0.75 µmol/l) peaked at 8 h after dosing. Free and glucuronidated conjugates of rosmarinic acid and methyl-rosmarinic acid, sulfated and glucuronidated conjugates of caffeic acid, and sulfated conjugates of ferulic acid were found in the urine. A total excretion of 5.47% of the dose of rosmarinic acid was excreted as these metabolites within 18 h after dosing; 83% of what was excreted occurred during the 8-18 h collection.

Rapid intestinal absorption of rosmarinic acid was found in another study in male Wistar rats.[44] Groups of three fasted rats were given a single dose by gavage of 100 µmol/kg bw rosmarinic acid in 10% propylene glycol, and blood samples were taken from the portal vein and abdominal artery at various intervals at up to 90 min after dosing. In the portal vein, the maximum serum concentration of intact rosmarinic acid was 1.36 µmol/l; this value was reached 10 min after dosing. The elimination half-life was 56.9 min. For the conjugates of rosmarinic acid, the maximum serum concentration was 0.86 µmol/l, reached 30 min after dosing. In the aortic artery, the maximum serum concentration of intact rosmarinic acid was 0.46 µmol/l; this value was reached 5 min after dosing, and the elimination half-life was 63.9 min. For the conjugates of rosmarinic acid, in the aortic artery, the maximum serum concentration was 0.9 µmol/l, also reached 30 min after dosing.

Parenteral

Rosmarinic Acid

Six male Sprague-Dawley rats received 250 µl of 980.37 µg [^{3}H]rosmarinic acid, i.v., providing a dose of 3.05 mg/kg.[41] Blood samples were taken at various intervals for 6 h. The concentration-time data were analyzed by a compartment model curve-fitting procedure; rosmarinic acid followed a two-compartment open model. The clearance phase half-life of rosmarinic acid was 1.8 h. The half-life for the fast disposition phase was less than 5 min; this distribution phase was completed in 0.75 h. The total body clearance was 115 ml/min/kg, and the mean residence time was 1.94 h. The absolute bioavailability, calculated using both i.v. and topical AUC corrected for dose and body wt, was 1.0. Examination of individual concentration-time profiles reported a small secondary peak found at the end of the fast disposition phase in four instances, and in three instances a slight, secondary peak was found in the slow disposition phase.

The researchers also examined the tissue distribution of [^{3}H]rosmarinic acid.[41] Three male Sprague-Dawley rats were dosed i.v. with 3 mg/kg [^{3}H]rosmarinic acid, and then killed 0.5 h after dosing. The greatest amounts of radioactivity were found in the lungs (0.94 µg/g), spleen (0.758 µg/g), heart (0.70 µg/g), and liver (0.510 µg/g); only 0.071 µg/g rosmarinic acid was recovered in the blood 0.5 h after dosing.

Penetration Enhancement

The effect of rosemary oil on the permeation of aminophylline (a compound used in cosmetic creams "to [reportedly] break down fat and cellulite from cells" and that is formed by combining the xanthene derivative theophylline with ethylene diamine in anhydrous alcohol) was determined in human skin *in vivo* using attenuated total refection Fourier transform infrared (ATR-FTIR) spectroscopy.[45] Rosemary oil did enhance the permeation of aminophylline; however, the increase in permeation was less than that observed with 50% ethanol.

TOXICOLOGICAL STUDIES

Single Dose (Acute) Toxicity

Single-dose toxicity studies are summarized in Table 9. The acute toxicity of Rosmarinus officinalis (rosemary)-derived ingredients is not very remarkable. The dermal LD_{50} of Rosmarinus officinalis (rosemary) leaf oil is > 10 ml/kg. The oral LD_{50} of Rosmarinus officinalis (rosemary) leaves is >2 g/kg, of Rosmarinus officinalis (rosemary) leaf extract is >8.5 g/kg, and of Rosmarinus officinalis (rosemary) leaf oil is 5.5 g/kg bw.

Repeated Dose Toxicity

Repeated-dose toxicity studies are summarized in Table 10. A number of oral repeated-dose toxicity studies were performed in mice and in rats with Rosmarinus officinalis (rosemary) leaves extracted in a number of solvents. Doses as high as 14.1 g/kg bw Rosmarinus officinalis (rosemary) leaf extract were tested (5 days by gavage), and studies were performed for up to

3 mos (dietary). Increases in absolute and relative liver-to-body weights were observed in many of the studies, independent of the extraction method; these changes were shown to be reversible, and no other signs of toxicity were observed. Oral administration of Rosmarinus officinalis (rosemary) leaf oil also affected liver weights. No signs of toxicity were observed when 0.3% rosmarinic acid was fed to C57BL/6J Min/+ (*Apc*^{Min}) mice for 8 wks.

In a clinical 21-day study with rosmarinic acid, nine patients with seasonal allergic rhinoconjunctivitis were treated orally with 50 mg/day and 10 were treated with 200 mg/day.[46] Ten controls were given a placebo. Patients recorded daily symptoms; no adverse events were reported and no significant abnormalities were detected in blood tests.

Ocular Irritation

Rosemary oil is reported to be a moderate ocular irritant.[26] (Details not provided.)

Anti-Inflammatory Effects

Rosmarinus Officinalis (Rosemary) Leaf Extract

Rosmarinus officinalis (rosemary) leaf extract has been shown to inhibit formaldehyde-induced plantar edema and phorbol 12-myristate 13-acetate (PMA)-, 12-tetradecanoylphorbol 13-acetate (TPA)-, and arachidonic acid-induced ear edema.[47,48]

In the formaldehyde-induced plantar edema study, groups of six male Balb/C mice were given an injection of 20 µl of 3% formaldehyde into the sub-plantar region of both hind paws.[47] After 2 h, one hind paw was treated with 10 µl of 12 mg/ml of an ethanol extract of Rosmarinus officinalis (rosemary) leaves topically, as an injection, or both. The mice were killed after 24 h. Topical administration reduced edema by 80%, the injection reduced it by 22%, and the combined application reduced edema by 24%.

The PMA-induced ear edema study was conducted in groups of 10 male Balb/c mice.[47] The effect of pretreatment with 10-1000 µg/cm^2 of an ethanol extract of Rosmarinus officinalis (rosemary) leaves at 30 min prior to induction of inflammation with 25ng/cm^2 PMA was evaluated. The mice were killed after 4 h. Doses of 100, 250, 500, and 1000 µg/cm^2 of the extract resulted in a statistically significant reduction of inflammation by 38, 79, 84, and 99%, respectively.

In a TPA-induced mouse ear edema study conducted in groups of six to 10 female CD-1 mice, a single dose of 20 µl acetone, 0.5 nmol TPA, or TPA and 0.04, 0.12, or 0.36 mg of a methanol extract of Rosmarinus officinalis (rosemary) leaves in 20 µl acetone was applied to one ear of each mouse.[48] The mice were killed after 5 h, and Rosmarinus officinalis (rosemary) leaf extract inhibited TPA-induced inflammation by 17, 75, and 92% respectively. The extract also inhibited TPA-induced erythema.

In the arachidonic acid-induced mouse ear edema study, 0.02, 0.09, or 0.45 mg of a methanol extract of Rosmarinus officinalis (rosemary) leaves in 20 µl acetone was applied to groups of 10 female CD-1 mice at 30 min prior to treatment with 0.3 mg arachidonic acid in 20 µl acetone. Inflammation was inhibited by 12, 28, and 54%, respectively.[48] The mice were killed after 1 h.

Rosmarinic Acid

Rosmarinic acid also has been shown to inhibit inflammation. In a TPA-induced mouse ear edema study, topical application of 1.35 ng/ear rosmarinic acid showed anti-inflammatory activity 5 h after TPA treatment.[46] Neutrophil infiltration was markedly inhibited.

Effect on Epidermal Hyperplasia

The dorsal skin of three to four CD-1 mice per groups was treated with either 200 µl acetone, 1 nmol TPA, or 1 nmol TPA and 3.6 mg Rosmarinus officinalis (rosemary) leaf extract in 200 µl acetone twice a day for 4 days.[48] Topical application of the extract with TPA inhibited a TPA-induced increase in the number of epidermal cell layers and epidermal thickness.

Immunologic Effects

An aq. extract of up to 2.5 mg/ml Rosmarinus officinalis (rosemary) leaves was found to inhibit ultraviolet (UV)-induced up-regulation of matrix metalloproteinase-1 (MMP-1) gene transcription in dermal human fibroblasts; the release of cytokines interleukin (IL)-1α and IL-6 was prevented by the extract.[49] Rosmarinic acid was found to induce melanogenesis in B16 melanoma cells; melanin content and tyrosinase expression were increased in a concentration-dependent manner.[50] The researchers stated that the induction of melanogenesis occurred through protein kinase A (PKA) activation signaling.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Non-Human

Rosmarinus Officinalis (Rosemary) Leaf Extract

Oral administration of Rosmarinus officinalis (rosemary) leaf extract adversely affected fertility in male rats.[51] Groups of 10 male Sprague Dawley rats were fed diet with 0, 250 or 500 mg/kg bw/day of an ethanol extract of Rosmarinus officinalis (rosemary) leaves in distilled water. After 53 days of dosing, each male rat was mated with two untreated female rats for 10 days; the female rats had been given a subcutaneous (s.c.) dose of 5.0 mg estradiol benzoate 54 h before and 0.5 mg

progesterone 6 h before being placed with the males. The males were dosed during, and killed after, the 10-day mating period, and the reproductive organs were examined. The females were killed 1 wk after removal of the males, and the reproductive tract of each female was examined to determine pregnancy and the number of implantation sites, viable fetuses, and fetal resorptions.

The body weights of male rats of the test groups were similar to those of controls. The absolute and relative organ to body weights of the testes, epididymides, seminal vesicles, ventral prostates, and vas deferens of the high dose animals were statistically significantly reduced compared to the controls. The sperm motility in cauda epididymides, sperm density, seminiferous tubule diameter, Leydig cell nuclear diameter, and epithelial height in epididymides and seminal vesicles were also statistically significantly reduced in the animals dosed with 500 mg/kg bw/day Rosmarinus officinalis (rosemary) leaf extract. Also in the high-dose group rats, germinal cells (i.e., spermatogonia, primary and secondary spermatocytes, and spermatids) and interstitial cells (i.e., fibroblasts and immature and mature Leydig cells) were statistically significantly decreased, and degenerating cells were statistically significantly increased. Clinical chemistry parameters were also evaluated; testosterone, follicle-stimulating hormone, and luteinizing hormone levels were statistically significantly decreased in high-dose male rats. Exposure to 500 mg/kg bw Rosmarinus officinalis (rosemary) leaf extract reduced fertility; the number of pregnant females was decreased in this group, there was a statistically significant decrease in the number of implantations and viable fetuses, and the total number of resorptions was statistically significantly increased. The same trends were generally found in the rats of the low-dose groups, but the changes did not reach statistical significance.

Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Extract

A group of 12 gravid female Wistar rats was dosed by gavage with 26 mg/day of a 30% aq. extract of Rosmarinus officinalis (rosemary) flower/leaf/stem extract (13 mg/ml solids) on days 1-6 of gestation (preimplantation), and a group of 14 gravid rats was dosed with the extract on days 6-15 of gestation (organogenesis).[52] Negative control groups of 12 or 11 gravid rats were given saline by gavage on days 1-6 or 6-15 of gestation, respectively. All dams were killed on day 21 of gestation. No signs of maternal toxicity were observed, and maternal weight gains were similar for treated and control groups.

In the rats dosed on days 1-6 of gestation, a non-statistically significant increase in preimplantation loss was observed. No changes in post-implantation loss were seen as compared to controls, and no other reproductive parameters were affected. In the group treated on days 6-15 of gestation, a non-statistically significant increase in post-implantation loss rate (2.54%) was reported; analysis of the resorptions found that they occurred during the early post-implantation period. No other changes in reproductive parameters were observed when compared to the negative control group. Developmental effects were not observed in either group.

Human

According to the *PDR for Herbal Medicines*, rosemary preparations should not be used as a drug during pregnancy.[53]
According to *Herbal Drugs and Phytopharmaceuticals*, toxic side effects may occur with components of the essential oil.[54]

Effects on Estrogenic Activity

Non-Human

Rosmarinus Officinalis (Rosemary) Leaf Extract

The effect of a methanol extract of Rosmarinus officinalis (rosemary) leaves on β-nicotinamide adenine dinucleotide phosphate (NADPH)-dependent microsomal metabolism of 17β-estradiol and estrone was evaluated in liver microsomes from female CD-1 mice.[55] The mice (number used not specified) had been fed a diet containing 2% of the extract for 3 wks. The control animals were fed a basal diet. [4-^{14}C]Estradiol, 20 or 50 µM, or [4-^{14}C]estrone, 20 µM, in ethanol (0.5 µCi) were used in the reaction mixture. With [4-^{14}C]estradiol, 2-hydroxyestradiol was the major metabolite in microsomes from both control and from Rosmarinus officinalis (rosemary) leaf extract-fed mice; the extract statistically significantly increased the formation of this metabolite by 137-139%. The extract also increased the formation of 2-hydroxyestrone by 140-156%, and the conversion of estradiol to 2-hydroxyestradiol + 2-hydroxyestrone was increased by 140-180% over controls. The formation of 16α-hydroxyestradiol was decreased by 50-63% in the Rosmarinus officinalis (rosemary) leaf extract group; the decrease (63%) was statistically significant with 20 µM estradiol. Other statistically significant changes were increases in the formation of 6α-hydroxyestradiol (60%); 6β-hydroxyestradiol (10%); and 6β-hydroxyestrone (117%).

With [4-^{14}C]estrone, 2-hydroxyestrone and 2-hydroxyestradiol were the major metabolites in the control and rosemary-treated microsomes; rosemary statistically significantly increased the formation of both of these metabolites by 143 and 156%, respectively. The conversion of estrone to 2-hydroxyestrone + 2-hydroxyestradiol by rosemary-treated microsomes was increased by 150-175%% over controls. The only other statistically significant change in rosemary-treated microsomes compared to controls was a 67% increase in the formation of 6β-hydroxyestrone. There was little or no conversion of estrone to 14α-hydroxyestradiol, 16α-hydroxyestradiol, or 4-hydroxyestradiol.

The researchers also examined the effect of Rosmarinus officinalis (rosemary) leaf extract on uridine-5'-diphosphoglucuronic acid (UDPGA)-dependent microsomal glucuronidation of estradiol and estrone. Administration of 2% Rosmarinus officinalis (rosemary) leaf extract to female CD-1 mice (number used not specified) in the diet for 3 wks statistically

significantly increased the rate of liver microsomal glucuronidation of estradiol (at pH 7.4 and 8.75) by 60-75% compared to untreated control values. The UDPGA-dependent microsomal glucuronidation of 4-nitrophenl was increased by <25%.

Groups of seven or eight 6-wk old ovariectomized CD-1 mice were fed a diet containing 2% of a methanol extract of Rosmarinus officinalis (rosemary) leaves or the basal diet.[55] After 3 wks, the animals were given an i.p. injection of 0, 45, or 100 ng/mouse estradiol or estrone in 50 µl corn oil, once daily for 3 days. Eighteen h after the last injection, the animals were killed and the uterus was removed. In the mice fed the basal diet, estradiol and estrone increased the uterine wet weight in a dose-dependent manner. Rosemary inhibited the uterine response in a statistically significant manner, with an inhibition of 35-50%.

Rosmarinic Acid

The mouse uterotrophic assay was conducted on rosmarinic acid in ovariectomized C57BL/6J mice.[56] Mice were dosed by gavage or s.c. with up to 1000 mg/kg bw/day rosmarinic acid for 7 days. 17α-Ethynyl estradiol was used as a reference control. Oral exposure did not have an agonistic or antagonistic effect. With s.c. administration, rosmarinic acid had an antagonistic effect. The lowest effect level (LOEL), defined as the lowest dose that induced significant change in uterine weight, was 300 mg/kg bw/day, s.c. The AN_{50} (interpolated dose that suppressed the uterotrophic effect of the reference 17α-ethynyl estradiol to 50% of the maximal uterine response) was 188 mg/kg bw/day, s.c.

Human

Rosmarinus Officinalis (Rosemary) Leaf Extract

In a study investigating the effects of a botanical supplement on sex steroid hormones and metabolic markers in premenopausal women, a few changes were found; overall, however, the changes were not very remarkable.[57] A group of 15 premenopausal women were asked to take a supplement containing 100 mg Rosmarinus officinalis (rosemary) leaf 5:1 extract; 100 mg *Curcurma longa* (turmeric) root extract standardized to 95% curcumin; 100 mg *Cyanara scolymus* (artichoke) leaf 6:1 extract; 100 mg *Silybum marinum* (milk thistle) seed extracted standardized to 80% silybin, silichristin, silidianin, and silymarin; 100 mg *Taraxacum officinalis* (dandelion) root 4:1 extract; and 50 mg *Schidandra chinensis* (berry) 20:1 extract. Four capsules were to be taken twice a day with meals. Rice powder placebo capsules were given to a group of 15 premenopausal women using the same dosing regimen. Blood and urine samples were collected during the early-follicular and mid-luteal phases of study menstrual cycles 1 and 5.

On average, test subjects took 6.3 capsules/day, and controls took 7.1 capsules/day. Compared to the placebo group, the following changes from Cycle 1 to Cycle 5 in early-follicular phase serum hormone concentrations were statistically significant or borderline significant: decreases in serum dehydroepiandrosterone (-13.2%, p= 0.02); dehydroepiandrosterone sulfate (-14.6%, p=0.07); androstenedione (-8.6%, p=0.05); and estrone sulfate (-12.0%, p=0.08). No other statistically significant changes or trends were observed for other serum sex steroid hormones, serum metabolic markers, or urinary estrogen metabolites at either phase.

GENOTOXICITY

Genotoxicity studies are summarized in Table 11. Rosmarinus officinalis (rosemary) leaf extract was not genotoxic when tested in *vitro* in an Ames test, in a chromosomal aberration assay in human lymphocytes, or in a gene-locus mutation assay in human lymphocytes, and it was not genotoxic when tested *in vivo* in a chromosomal aberration assay or micronucleus test. Various extraction solvents were used. Rosmarinus officinalis (rosemary) leaf oil was not mutagenic *in vitro* in an Ames test. However, *in vivo*, oils that were extracted by hydrodistillation did induce statistically significant increases in chromosomal aberrations without gaps in a chromosomal aberration assay at 2000 mg/kg bw, increases in micronucleated polychromatic erythrocytes (MNPCEs) in several micronucleus tests at 1000 and 2000 mg/kg bw, and increases in DNA damage in a comet assay at ≥300 mg/kg bw; no genotoxic effects were seen in a micronucleus test at 1500 mg/kg bw/day with leaves extracted using absolute ethanol. Rosmarinic acid was not genotoxic *in vitro* or *in vivo* in micronucleus tests or comet assays. A mixture containing 19% Rosmarinus officinalis (rosemary) leaves, 71.5% St. John's Wort, and 9.5% spirulina (algae) induced statistically significant increases in MNPCEs at 760 and 1520 mg/kg bw/day in a micronucleus test; in frequency of aneuploidy, percent polyploidy, and total percent aberrations with 760 and 1520 mg/kg bw/day in a chromosomal aberration assay; and in frequency of banana-shaped, swollen achrosome, and triangular head sperm abnormalities and percent total spermatozoa abnormalities at 1520 mg/kg bw/day in a spermatozoa abnormality assay. *In vitro*, Rosmarinus officinalis (rosemary) leaf extract and rosmarinic acid were shown to have anti-mutagenic potential. *In vivo* in micronucleus assays, rosmarinic acid, but not Rosmarinus officinalis (rosemary) leaf extract, decreased the number of MNPCEs induced by a genotoxic agent.

CARCINOGENICITY

Anti-Tumor Activity

Anti-tumor activity studies are summarized in Table 12. Topical application of methanol and double distilled water extracts of Rosmarinus officinalis (rosemary) leaves, and orally administered rosmarinic acid (by gavage), statistically significantly

decreased skin tumors in mice; in these studies, 7,12-dimethylbenz[a]anthracene (DMBA) or benzo[a]pyrene (B(a)P)was used for initiation and TPA or croton oil was used for promotion. Dietary administration of Rosmarinus officinalis (rosemary) leaf extract decreased the incidence of palpable mammary tumors in rats caused by DMBA. Rosmarinic acid, dosed by gavage, completely prevented the formation of oral squamous cell carcinoma in a DMBA-induced hamster buccal pouch carcinogenicity study. Dietary rosmarinic acid (0.3%) did not inhibit colorectal tumor formation in mice.

IRRITATION AND SENSITIZATION

Skin Irritation/Sensitization

Non-Human

Rosmarinus Officinalis (Rosemary) Leaf Oil

An ointment containing 4.4% Rosmarinus officinalis (rosemary) leaf oil (and other essential oils) was not irritating to rat skin.[58] The ointment was applied to the shaved skin of Lewis rats twice daily, for 14 days, at concentrations up to 40%. No gross or microscopic lesions were reported.

Rosmarinus officinalis (rosemary) leaf oil, applied undiluted to intact and abraded rabbit skin under occlusion, was moderately irritating.[59] No details were provided.

Rosmarinic Acid

Rosmarinic acid was predicted to be not irritating in an *in vitro* reconstituted human epidermis model for skin irritation.[60] Rosmarinic acid, isolated from *Melissa officinalis* L., was dissolved in a phosphate buffer solution and tested at a concentration of 1% (27.7 mM). The solution was applied to the tissue for 15 min, and the tissue was evaluated after 42 h. There were no statistically significant effects on epidermis viability, release of interleukin-1α, or trans-epithelial electrical resistance (TEER) values when compared to the vehicle control.

Human

Rosmarinus Officinalis (Rosemary) Leaf Extract

The irritation potential of *Rosmarinus officinalis* (rosemary) leaves, tested undiluted with sufficient petrolatum for binding, was evaluated in a patch test in 234 patients with contact dermatitis or eczema.[61] Of the 234 subjects tested, 21 had +/- reactions, 18 had a + reaction, and 5 had a ++ reaction. No subjects had a +++ reaction.

The dermal irritation potential of Rosmarinus officinalis (rosemary) leaves, extracted with supercritical CO_2, as a concrete (insoluble waxes) extracted in hexane, and as an absolute (soluble in hexane) and a concrete (insoluble waxes) extracted in hexane, was evaluated in epicutaneous tests.[16] Each test substance was applied undiluted in petrolatum on three sites using Finn chambers. The absolute was tested in 25 subjects, and the other two extracts were tested in 20 subjects. The supercritical CO_2 extract of Rosmarinus officinalis (rosemary) leaves produced 1/20 positive reactions and the absolute produced 2/25 positive reactions; both were considered weak irritants. The concrete did not induce any irritation reactions.

Rosmarinus Officinalis (Rosemary) Leaf Oil

Rosmarinus officinalis (rosemary) leaf oil, tested at a concentration of 10% in petrolatum, was not an irritant in a 48-h closed patch test (number of subjects not specified), and it was not a sensitizer in a maximization study in 25 subjects.[59] No other details were provided.

Phototoxicity

Rosmarinus Officinalis (Rosemary) Leaf Extract

The phototoxicity of Rosmarinus officinalis (rosemary) leaf extract, extracted with supercritical CO_2, as a concrete extracted in hexane, and as an absolute and a concrete extracted in hexane, was evaluated as a part of the epicutaneous irritation test described above.[16] Photopatch tests were performed on two of the three test sites; one site was irradiated with 10 J/cm^2 UVA and the second site with 75% of the minimal erythema dose of UVB. The test sites were scored after 48 and 72 h, and were compared to the non-irradiated site. None of the extracts were phototoxic.

Case Reports

Several cases of allergic reactions to *Rosmarinus officinalis* (rosemary) have been reported, and are summarized in Table 13.[62-70] In some of the studies, follow-up patch testing included photopatch tests; generally, reactions were stronger in the photopatch tests, compared to standard testing.[66,67] Some of the follow-up patch testing included carnosol; testing with carnosol resulted in positive reactions.[63,67]

SUMMARY

This report addresses 12 Rosmarinus officinalis (rosemary)-derived as used in cosmetics. Most of the ingredients included in this review are extracts, oils, powders, solutions, or waxes derived from a defined part of the Rosmarinus officinalis (rosemary) plant. Rosmarinic acid is a constituent of the plant as well as a cosmetic ingredient. The Rosmarinus officinalis (rosemary)-derived ingredients are reported to have a number of functions, and the most common functions in cosmetics are as a

skin conditioning agent or as a fragrance ingredient, and three of the ingredients are reported to function as antioxidants. According to VCRP data obtained from the FDA, Rosmarinus officinalis (rosemary) leaf extract has the most uses, 689, followed by Rosmarinus officinalis (rosemary) leaf oil, which has 516 uses. Most of the reported use concentrations for Rosmarinus officinalis (rosemary)-derived ingredients are well below 0.1%. However, Rosmarinus officinalis (rosemary) leaf extract has higher concentrations of use reported, specifically, use at up to 10% in body and hand products and 3% in eye shadow formulations and bath soaps and detergents. Three of the ingredients are not reported to be used.

Rosmarinus officinalis (rosemary) extract is prepared by extraction from the leaves of Rosmarinus officinalis with acetone, ethanol, hexane, a combination of hexane and ethanol (in a two-step process), or supercritical CO_2; it can also be prepared from a deodorized or partially deodorized ethanol extract of rosemary. Additional methods include extraction with absolute ethanol (resulting in an absolute) or a collection of the insoluble waxes (resulting in a concrete).

Rosmarinus officinalis L. is composed of an array of constituents, primarily phenolic acids, flavonoids, monoterpenes, diterpenes, diterpenoids, triterpenes, and rosmarinic acid. The principal antioxidative components of Rosmarinus officinalis (rosemary) leaf extract are the phenolic diterpenes carnosol and carnosic acid. The actual amount of constituents present varies according to the stage of development, variety of plant, season harvested, origin of the leaves, and extraction method.

Rosmarinic acid is present in many plants; it occurs in the Lamiaceae and the Boraginaceae families. It is present in *Rosmarinus officinalis*, *Melissa officinalis*, *Ocimum basilisum*, *Perilla frutescens*, *Artemisia capillaris*, *Calendula officinalis* L., *Salvia officinalis*, and in ferns of the Blechnaceae family.

In an *in vitro* transdermal permeation study using full-thickness dorsal rat skin, rosmarinic acid had good permeability through the skin. The permeability was determined using both aqueous and ethanol solvents; permeation of rosmarinic acid across excised rat skin was higher from the ethanol solution than from the aqueous solution. Rosmarinic acid is absorbed through mouse skin; absolute bioavailability was 60% after 12 h. Rosmarinic acid was found in the skin, muscle, and bone of rats 4.5 h after occlusive application.

Oral administration of rosmarinic acid resulted in rapid intestinal absorption, and it was metabolized into conjugated and/or methylated forms. In a study in which rats were dosed by gavage with 200 mg/kg rosmarinic acid as a 20% ethanol solution, approximately 32% of the dose was excreted in the urine; seven metabolites were isolated, and only 0.08% of the dose was excreted as unchanged rosmarinic acid. Following i.v. dosing with rosmarinic acid in rats, rosmarinic acid followed a two-compartment open model; he clearance phase half-life 1.8 h, the distribution phase was completed in 0.75 h, and the total body clearance was 115 ml/min/kg.

Rosemary oil increased the permeation of aminophylline through human skin, but the increase was not as great as that seen with 50% ethanol.

The acute toxicity of Rosmarinus officinalis (rosemary)-derived ingredients is not very remarkable. The dermal LD_{50} of Rosmarinus officinalis (rosemary) leaf oil is > 10 ml/kg. The oral LD_{50} of Rosmarinus officinalis (rosemary) leaves is >2 g/kg, of Rosmarinus officinalis (rosemary) leaf extract is >8.5 g/kg, and of Rosmarinus officinalis (rosemary) leaf oil is 5.5 g/kg bw.

A number of oral repeated-dose toxicity studies were performed in mice and in rats with Rosmarinus officinalis (rosemary) leaves extracted in a various solvents. Doses as high as 14.1 g/kg bw Rosmarinus officinalis (rosemary) leaf extract were tested (5 days by gavage), and studies were performed for up to 3 mos (dietary). Increases in absolute and relative liver-to-body weights were observed in many of the studies, independent of the extraction method; these changes were shown to be reversible, and no other signs of toxicity were observed. Oral administration of Rosmarinus officinalis (rosemary) leaf oil also affected liver weights. No signs of toxicity were observed when 0.3% rosmarinic acid was fed to C57BL/6J Min/+ (Apc^{Min}) mice for 8 wks. In a clinical 21-day study, daily oral treatment with 50 or 200 mg rosmarinic acid did not produce any adverse effects.

Rosmarinus officinalis (rosemary) leaf extract and rosmarinic acid have been shown to have anti-inflammatory activity. Rosmarinus officinalis (rosemary) leaf extract inhibited a TPA-induced increase in the number of epidermal cell layers and epidermal thickness in mouse skin.

According to the *PDR for Herbal Medicines*, rosemary preparations should not be used as a drug during pregnancy. Dietary administration of an ethanol extract of Rosmarinus officinalis (rosemary) leaf adversely affected fertility in male rats. The absolute and relative organ to body weights of the testes, epididymides, seminal vesicles, ventral prostates, and vas deferens of rats dosed with 500 mg/kg bw/day of the extract were statistically significantly decreased compared to the vehicle controls. Also at that dose level, a reduction in fertility was observed; the number of pregnant females was decreased, there was a statistically significant decrease in the number of implantations and in viable fetuses, and the total number of resorptions was statistically significantly increased. The same trends were generally found in the rats of the low-dose groups, but the changes did not reach statistical significance. In a study in which gravid female Wistar rats was dosed by gavage with 26 mg/day of a 30% aq. extract of Rosmarinus officinalis (rosemary) flower/leaf/stem extract during preimplantation or during organogenesis, no statistically significant changes were observed.

The NADPH-dependent microsomal metabolism of 17β-estradiol and estrone was evaluated in liver microsomes from mice fed 2% of a methanol extract of Rosmarinus officinalis (rosemary) leaves for 3 wks. With [4-^{14}C]Estradiol, the extract statistically significantly increased the formation of 2-hydroxyestradiol and 2-hydroxyestrone, With [4-^{14}C]estrone, the extract statistically significantly increased the formation of 2-hydroxyestrone and 2-hydroxyestradiol, and the conversion of estrone to 2-hydroxyestrone + 2-hydroxyestradiol. In an assay examining the effect of Rosmarinus officinalis (rosemary) leaf extract on UDPGA-dependent microsomal glucuronidation of estradiol and estrone, administration of 2% Rosmarinus officinalis (rosemary) leaf extract to female CD-1 mice in the diet for 3 wks statistically significantly increased the rate of liver microsomal glucuronidation of estradiol compared to untreated control values. In a dietary study in ovariectomized CD-1 mice, 2% of a methanol extract of Rosmarinus officinalis (rosemary) leaves inhibited the uterine response in a statistically significant manner. In a mouse uterotrophic assay with rosmarinic acid in ovariectomized C57BL/6J mice, s.c. administration, but not oral administration, had an antagonistic effect. The LOEL was 300 mg/kg bw/day s.c. rosmarinic acid; the AN_{50} was 188 mg/kg bw/day, s.c.

In a clinical study investigating the effects on sex steroid hormones and metabolic markers of a botanical supplement containing 100 mg Rosmarinus officinalis (rosemary) leaf 5:1 extract (and other botanical ingredients) in premenopausal women, a few changes were found. Overall, the changes were not very remarkable.

Rosmarinus officinalis (rosemary) leaf extract was not genotoxic when tested in *vitro* in an Ames test, in a chromosomal aberration assay in human lymphocytes, or in a gene-locus mutation assay in human lymphocytes, and it was not genotoxic when tested *in vivo* in a chromosomal aberration assay or micronucleus test. Various extraction solvents were used. Rosmarinus officinalis (rosemary) leaf oil was not mutagenic *in vitro* in an Ames test. However, *in vivo*, oils that were extracted by hydrodistillation did induce statistically significant increases in chromosomal aberrations without gaps in a chromosomal aberration assay at 2000 mg/kg bw, increases in MNPCEs in several micronucleus tests at 1000 and 2000 mg/kg bw, and increases in DNA damage in a comet assay at ≥300 mg/kg bw; no genotoxic effects were seen in a micronucleus test at 1500 mg/kg bw/day with an oil that was extracted using absolute ethanol. Rosmarinic acid was not genotoxic *in vitro* or *in vivo* in micronucleus tests or comet assays. A mixture containing 19% Rosmarinus officinalis (rosemary) leaves, 71.5% St. John's Wort, and 9.5% spirulina (algae) induced statistically significant increases in MNPCEs at 760 and 1520 mg/kg bw/day in a micronucleus test; in frequency of aneuploidy, percent polyploidy, and total percent aberrations with 760 and 1520 mg/kg bw/day in a chromosomal aberration assay; and in frequency of banana-shaped, swollen achrosome, and triangular head sperm abnormalities and percent total spermatozoa abnormalities at 1520 mg/kg bw/day in a spermatozoa abnormality assay. *In vitro*, Rosmarinus officinalis (rosemary) leaf extract and rosmarinic acid were shown to have anti-mutagenic potential. *In vivo* in micronucleus assays, rosmarinic acid, but not Rosmarinus officinalis (rosemary) leaf extract, decreased the number of MNPCEs induced by a genotoxic agent.

Topical application of methanol and double distilled water extracts of Rosmarinus officinalis (rosemary) leaves, and orally administered rosmarinic acid (by gavage), statistically significantly decreased skin tumors in mice; in these studies, DMBA or benzo[a]pyrene was used for initiation and TPA or croton oil was used for promotion. Dietary administration of Rosmarinus officinalis (rosemary) leaf extract decreased the incidence of palpable mammary tumors in rats caused by DMBA. Rosmarinic acid, administered by gavage, completely prevented the formation of oral squamous cell carcinoma in a DMBA-induced hamster buccal pouch carcinogenicity study. Dietary rosmarinic acid (0.3%) did not inhibit colorectal tumor formation in mice.

An ointment containing 4.4% Rosmarinus officinalis (rosemary) leaf oil (and other essential oils), applied at concentrations up to 40%, was not irritating to rat skin. However, in a rabbit study, occlusive application to intact and abraded skin produced moderate irritation. In an *in vitro* study using the reconstituted human epidermis model, rosmarinic acid was not predicted to be irritating. In clinical testing, Rosmarinus officinalis (rosemary) leaves produced irritation (scores of +/-, +, or ++) in 44/234 patients with contact dermatitis or eczema. A supercritical extract and the absolute of Rosmarinus officinalis (rosemary) leaves were considered weak irritants in a small study with test populations of 20-25 subjects; the extracts were not phototoxic. Rosmarinus officinalis (rosemary) leaf oil, 10% in petrolatum, was not an irritant in a 48-h closed patch test, or a sensitizer in a maximization study.

Several cases of allergic reactions to *Rosmarinus officinalis* (rosemary) have been reported. In some of the studies, follow-up patch testing included photopatch tests; generally, reactions were stronger in the photopatch tests, compared to standard testing. Some also evaluated the effect of carnosol; testing with carnosol resulted in positive reactions.

DISCUSSION

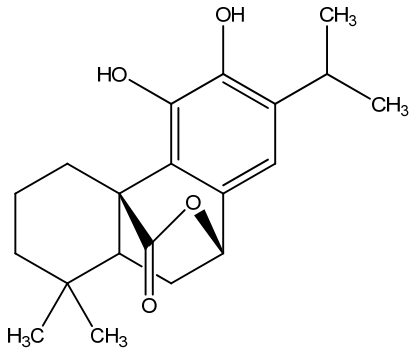
To be developed.

CONCLUSION

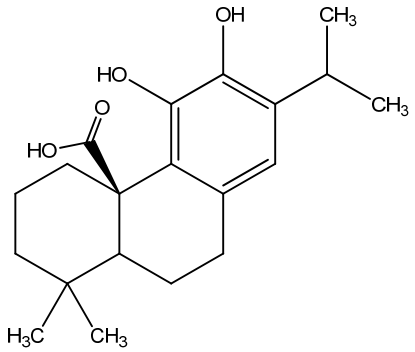
To be determined.

FIGURES

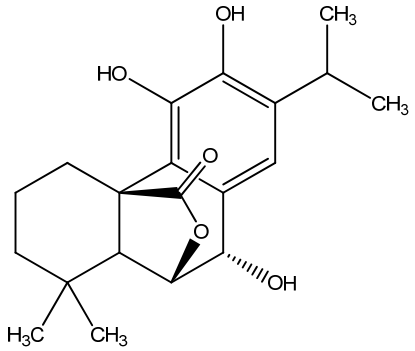
Figure 1. Principal diterpenes



1a. Carnosol

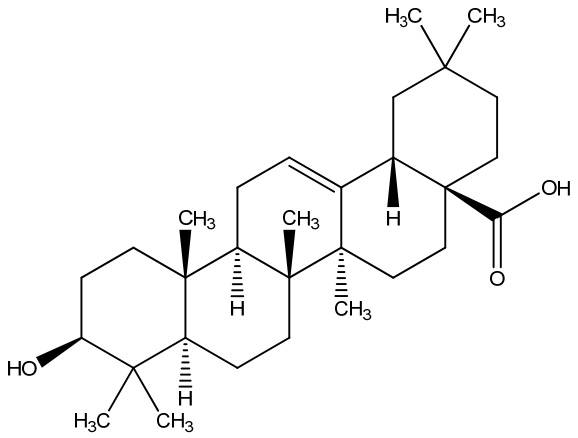


1b. Carnosic acid

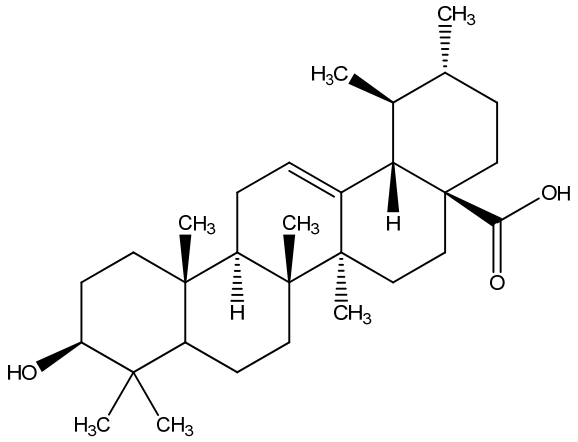


1c. Rosmanol

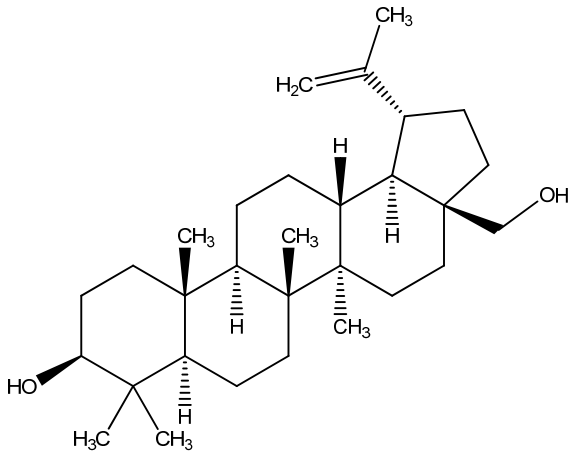
Figure 2. Principal triterpenes



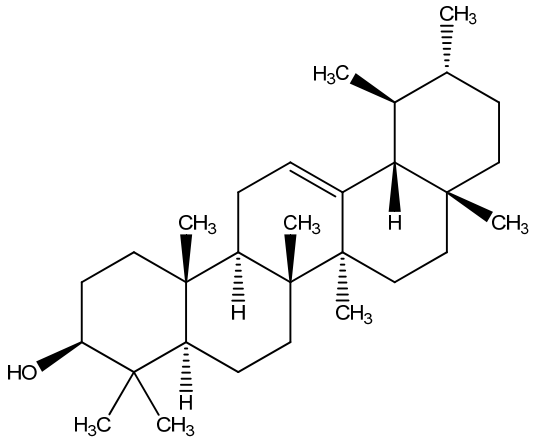
2a. Oleanolic acid



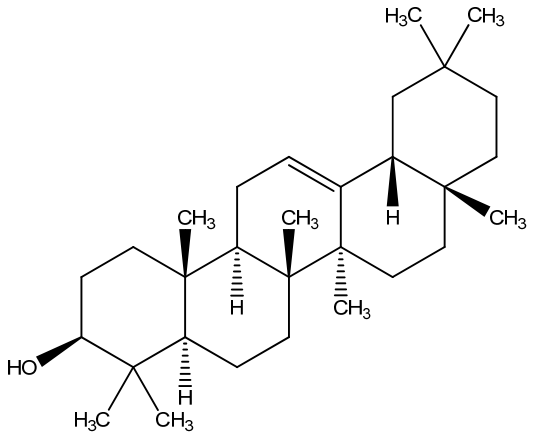
2b. Ursolic acid



2c. Betulin

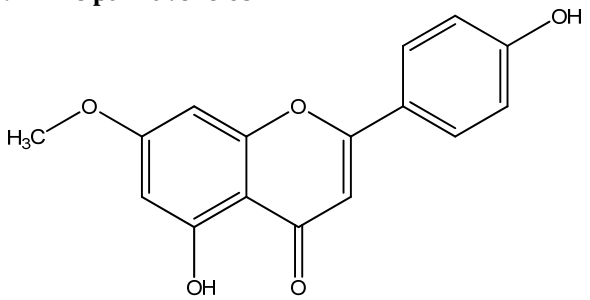


2d. α-Amyrin

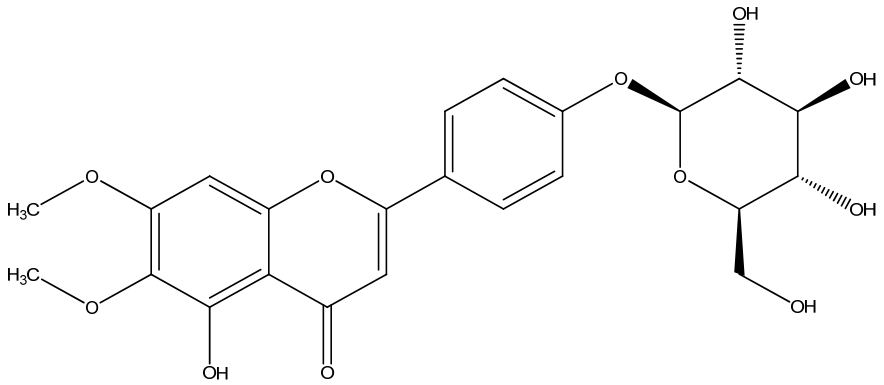


2e. β-Amyrin

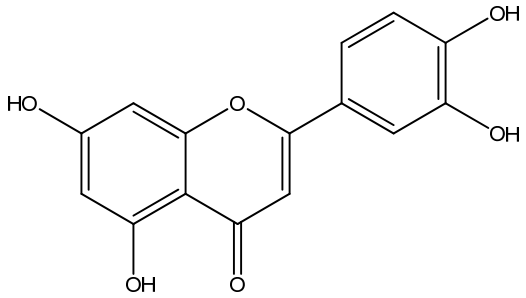
Figure 3. Principal flavonoids



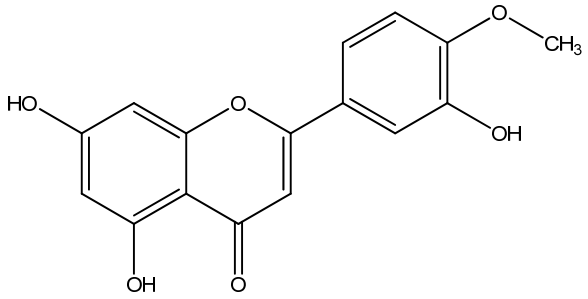
3a. Genkwanin



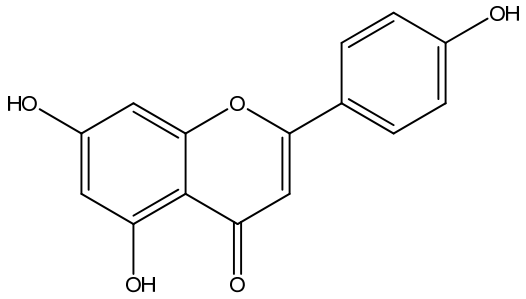
3b. Cirsimarin



3c. Luteolin

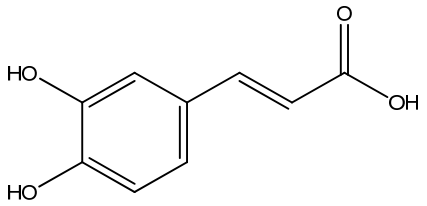


3d. Diosmetin

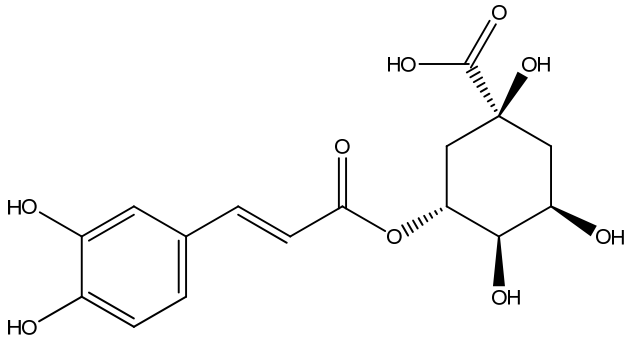


3e. Apigenin

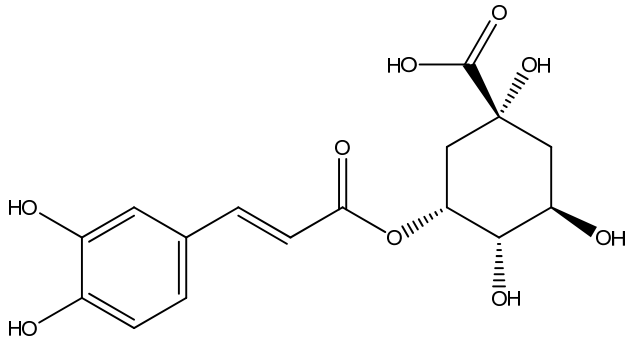
Figure 4. Phenolic acids



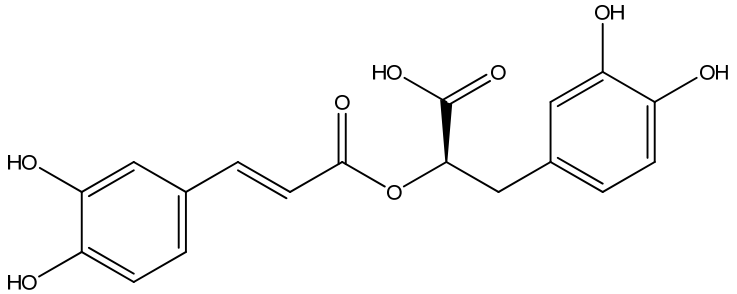
4a. Caffeic acid



4b. Chlorogenic acid

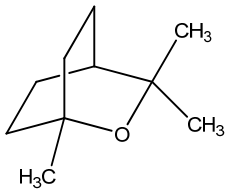


4c. Neochlorogenic acid

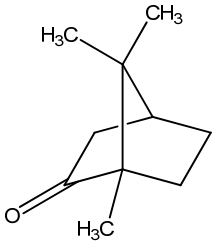


4d. Labiatic acid

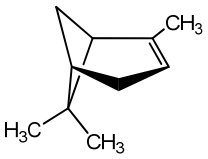
Figure 5. Principal Volatiles



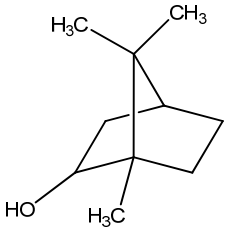
5a. 1,8-Cineole



5b. Camphor



5c. α-Pinene



5d. Borneol

TABLES

Table 1. Definitions, Reported Functions, and Chemical Class

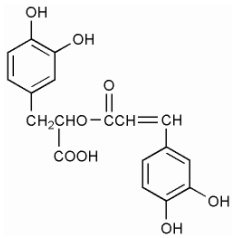
Ingredient (CAS No.)	Definition[1]	Reported Function(s)[1]	Chemical Class[1]
Rosmarinus Officinalis (Rosemary) Extract (84604-14-8)	the extract of the whole plant *Rosmarinus officinalis*	skin-conditioning agent – misc	botanical products and botanical derivatives
Rosmarinus Officinalis (Rosemary) Flower Extract	the extract of the flowers of *Rosmarinus officinalis*	antioxidant; deodorant agents; skin-conditioning agents – misc	botanical products and botanical derivatives
Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Extract	the extract of the flowers, leaves and stems of *Rosmarinus officinalis*	fragrance ingredients; skin-conditioning agents - misc	botanical products and botanical derivatives
Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Water	the aqueous solution of the steam distillates obtained from the flowers, leaves and stems of *Rosmarinus officinalis*	fragrance ingredient	essential oils and waters
Rosmarinus Officinalis (Rosemary) Flower Wax	wax obtained from the flower of *Rosmarinus officinalis*	fragrance ingredient	waxes
Rosmarinus Officinalis (Rosemary) Leaf	the leaf of *Rosmarinus officinalis*	skin-conditioning agents – misc	botanical products and botanical derivatives
Rosmarinus Officinalis (Rosemary) Leaf Extract (84604-14-8)	the extract of the leaves of *Rosmarinus officinalis*	antimicrobial agents; antioxidant; fragrance ingredients; skin-conditioning agents - miscellaneous; skin-conditioning agents – occlusive	botanical products and botanical derivatives
Rosmarinus Officinalis (Rosemary) Leaf Oil (8000-25-7)	the essential oil obtained from the flowering tops and leaves of *Rosmarinus officinalis*	fragrance ingredients; skin-conditioning agents – misc	essential oils and waters
Rosmarinus Officinalis (Rosemary) Leaf Powder	the powder derived from the dried, ground leaves of *Rosmarinus officinalis*	flavoring agents	botanical products and botanical derivatives
Rosmarinus Officinalis (Rosemary) Leaf Water	an aqueous solution of the steam distillate obtained from the leaves of *Rosmarinus officinalis*	fragrance ingredient	essential oils and waters
Rosmarinus Officinalis (Rosemary) Water	an aqueous solution of the steam distillate obtained from *Rosmarinus officinalis*	fragrance ingredient	essential oils and waters
Rosmarinic Acid (20283-92-5)	the acid obtained from *Melissa officinalis* or *Rosmarinus officinalis*; it conforms to the structure: 	antioxidant	carboxylic acids (excluding salts)

Table 2. Chemical and Physical Properties

Property	Description	Reference
	Rosmarinus Officinalis (Rosemary) Leaf	
odor	strongly aromatic	40
	Rosmarinus Officinalis (Rosemary) Leaf Extract	
physical state and appearance	powder or liquid	11
	colorless, volatile oil	12
	dark brown viscous liquid with a characteristic smell and taste (as the extract (and) Helianthus Annuus Seed Oil)	13,14
solubility	insoluble in water	11
refractive index	1.4710 - 1.4740	22
density	0.9165 - 0.9220	22
	Rosmarinus Officinalis (Rosemary) Leaf Oil	
physical state and appearance	colorless or pale yellow liquid with characteristic odor and a warm, camphoraceous taste	17,39
	colorless, pale yellow, or pale green liquid with a camphorous odor	71
solubility	almost insoluble in water	39
	soluble in most vegetable oils; insoluble in alcohol and in propylene glycol	17
density (d^{25}_{25})	0.894-0.912	***39***
	0.907-0.920	71
index of refraction (n_D^{20})	1.464-1.476	39
	Rosmarinus Officinalis (Rosemary) Leaf Powder	
physical state and appearance	greyish-green to yellowish-green powder	40
	Rosmarinic Acid	
physical state and appearance	white crystalline powder	8
	clear brownish liquid (aq. extract)	20
molecular weight	360.31	72
melting point	172-172°C	8
	171-175°C	72
boiling point	694.7±55.0°C (calculated)	73
solubility	soluble in water up to 2%	20
density	0.98-0.99 (aq. extract)	20
octanol/water partition coefficient	0.21 ± 0.01	44
log P	0.871±0.397 (25°C; calculated)	73
optical rotation $[\alpha]_D25$	+39.2° (c = 1.0 in methanol)	8
pKa	2.78±0.10 (25°C; calculated)	73

Table 3. Chemical constituents by plant part [74]

Constituent*	Plant	Leaf	Flower	Shoot	Resin, Exudate, Sap	Essential Oil	Tissue Culture
carbohydrates	640,600-704,660	-	-	-	-	-	-
fiber	165,420-206,338	-	-	-	-	-	-
fat	134,020-187,418	-	-	-	-	-	-
water	77,900-108,300	-	-	-	-	-	-
ash	61,900-75,570	-	-	-	-	-	-
protein	40,700-62,568	-	-	-	-	-	-
ursolic acid	28,000-41,000	-	-	20	-	-	-
rosmarinic acid	25,000	3500	-	13,500	-	-	38,957
EO	3300-25,000	-	-	-	-	-	-
calcium	10,919-16,150	-	-	-	-	-	-
potassium	8842-11,284	-	-	-	-	-	-
oleanolic acid	10,500	-	-	20	-	-	-
carnosol	-	530-9803					
cineole	168-9728	-	-	-	-	-	-
1,8-cineole	8125	-	-	-	-	-	-
camphor	60-5800	-	-	-	-	-	-
myrcene	25-5605	-	-	-	-	-	-
bornyl acetate	5054	-	-	-	-	-	-
α –pinene	235-4750	-	-	-	-	-	-
borneol	12-4237	-	-	-	-	-	-
magnesium	2142-2483	-	-	-	-	-	-
rosmaric acid	3000-3500	-	-	-	-	-	-
camphene	23-2350	-	-	-	-	-	-
β-caryophyllene	12-2075	-	-	70-2075			
toluene	436-2071	-	-	-	-	-	-
limonene	1950	-	-	-	-	-	-
α –terpineol	24-1555	-	-	-	-	-	-
β-pinene	17-1425	-	-	-	-	-	-
phosphorus	490-1000	-	-	-	-	-	-
p-cymene	25-950	-	-	-	-	-	-
carvone	16-760	-	-	-	-	-	-
α-humulene	-	-	-	725			
salicylates	-	70-680	-	-	-	-	-
ascorbic acid	612-673	-	-	-	-	-	-
α-amorphene	70-665	-	-	-	-	-	-
γ-muurolene	70-665	1	-	-	-	-	-
phytosterols	580-640	-	-	-	-	-	-
sodium	462-592	-	-	-	-	-	-
linalol	585	-	-	-	-	-	-
α –terpinene	4-555	-	-	-	-	-	-
terpinen-4-ol	4-521	-	-	-	-	-	-
α –thujene	1-475	-	-	-	-	-	-
δ-terpineol	7-418	-	-	-	-	-	-
iron	220-400	-	-	-	-	-	-
α –thujone	84-399	-	-	-	-	-	-
(E)-β-ocimene	-	-	-	380			
verbenone	10-375	-	-	-	-	-	-
geraniol	50-370	-	-	-	-	-	-
3-hexanone	74-351	-	-	-	-	-	-
terpinolene	12-350	-	-	-	-	-	-
caryophyllene	16-340	-	-	-	-	-	-
δ-3-carene	330	-	-	-	-	-	-
fenchone	250	-	-	-	-	-	-
β-thujone	11-209	-	-	-	-	-	-
β-elemene	-	-	-	3-200			
sabinene	190	-	-	-	-	-	-
mesityl alcohol	40-190	-	-	-	-	-	-
linalol acetate	32-152	-	-	-	-	-	-
α –phellandrene	133	-	-	-	-	-	-
α- fenchyl alcohol	28-133	-	-	-	-	-	-
p-menth-3-en-1-ol	28-133	-	-	-	-	-	-
3,5,5-trimethylhexan-1-ol	28-133	-	-	-	-	-	-
trans-ocimene	4-130	-	-	-	-	-	-
cis-pinan-3-one	-	17-110	-	-	-	-	-
4-terpinenyl-acetate	-	12-110	-	-	-	-	-
safrole	32-95	-	-	-	-	-	-
cis-β-terpineol	20-95	-	-	-	-	-	-

Table 3. Chemical constituents by plant part [74]

Constituent*	Plant	Leaf	Flower	Shoot	Resin, Exudate, Sap	Essential Oil	Tissue Culture
α- fenchyl acetate	20-95	-	-	-	-	-	-
longifolene	20-95	-	-	-	-	-	-
isoborneol	7-95	-	-	-	-	-	-
rosmanol	-	92	-	-	-	-	-
(+)-limonene	16-76	-	-	-	-	-	-
δ-cadinene	75	-	-	-	-	-	-
caryophyllene oxide	75	-	-	-	-	-	-
(Z)-β-ocimene	-	-	-	75	-	-	-
trans-pinocarveol	-	32-42	-	-	-	-	-
3-octanone	20-40	-	-	-	-	-	-
boron	22-39	-	-	-	-	-	-
zinc	30-38	-	-	-	-	-	-
AR-curcumene	8-38	-	-	-	-	-	-
methyl heptenone	8-38	-	-	-	-	-	-
myrtenol	8-38	-	-	-	-	-	-
lavandulol	7-34	-	-	-	-	-	-
trans-β-terpineol	7-34	-	-	-	-	-	-
trans-myrtenol	-	32	-	-	-	-	-
benzyl alcohol	7-32	-	-	-	-	-	-
elemol	7-32	-	-	-	-	-	-
γ-eudesmol	7-32	-	-	-	-	-	-
rosmadial	-	30	-	-	-	-	-
α-amyrenone	-	-	-	30	-	-	-
β-amyrenone	-	-	-	30	-	-	-
epirosmanol	-	26	-	-	-	-	-
β-carotene	19-21	-	-	-	-	-	-
rofficerone	-	-	-	20	-	-	-
trans-sabinene hydrate	19	-	-	-	-	-	-
manganese	18-19	-	-	-	-	-	-
cis-α-bisabolene	4-19	-	-	-	-	-	-
isopinocarveol	4-19	-	-	-	-	-	-
isopulegol	4-19	-	-	-	-	-	-
3-octanol	4-19	-	-	-	-	-	-
dimethyl styrene	1-19	-	-	-	-	-	-
7-methoxy-rosmanol	-	-	-	18			
isorosmanol	-	-	17	-	-	-	-
cis-myrtenol	-	11-17	-	-	-	-	-
cisimaritrin	-	-	-	16	-	-	-
α-amyrin	NS	-	-	13	-	-	-
β-amyrin	NS	-	-	13	-	-	-
botulin	-	-	-	12.1	-	-	-
α –muurolene	NS	2-12	-	-	-	-	-
3-o-acetyloleanolic acid	-	-	-	11	-	-	-
3-o-acetylursolic acid	-	-	-	11	-	-	-
niacin	10-11	-	-	-	-	-	-
peperitenone	-	4-8	-	-	-	-	-
eugenol methyl ether	-	5-7	-	-	-	-	-
copper	5-6	-	-	-	-	-	-
thiamin	5-6	-	-	-	-	-	-
carvacrol	NS	5-6	-	-	-	-	-
α -terpinenyl acetate	-	5-6	-	-	-	-	-
allo-aromadendrene	-	4-5	-	-	-	-	-
neo-thujol	-	1.5-5	-	-	-	-	-
calamenene	1-5	-	-	-	-	-	-
trans-carveol	1-5	-	-	-	-	-	-
p-cymen-8-ol	1-5	-	-	-	-	-	-
nopol	1-5	-	-	-	-	-	-
γ-candinene	NS	1-5	-	-	-	-	-
α-copaene	-	2-4	-	-	NS	-	-
epi- α -bisabolol	-	3	-	-	-	-	-
sabinyl acetate	-	1.5	-	-	-	-	-
β-gurjunene	-	0.5	-	-	-	-	-
cis-sabinene hydrate	NS	0.4	-	-	-	-	-
β-phellandrene	trace	-	-	-	-	-	-
tricyclene	trace	-	-	-	-	-	-
α-fenchol	-	trace	-	-	-	-	-
p-menth-cis-en-1-ol	-	trace	-	-	-	-	-

Table 3. Chemical constituents by plant part [74]

Constituent*	Plant	Leaf	Flower	Shoot	Resin, Exudate, Sap	Essential Oil	Tissue Culture
p-menth-trans-en-1-ol	-	trace	-	-	-	-	-
trans-anethole	NS	-	-	-	-	-	-
apigen-7-glucoside	NS	-	-	-	-	-	-
betulin	NS	-	-	-	-	-	-
bornylene	NS	-	-	-	-	-	-
cadalene	NS	-	-	-	-	-	-
caffeic acid	NS	-	-	-	-	-	-
calacorene	NS	-	-	-	-	-	-
carnosic acid	NS	-	-	-	-	-	-
chlorogenic acid	NS	-	-	-	-	-	-
cirsilion	NS	-	-	-	-	-	-
cubenene	NS	-	-	-	-	-	-
diosmetin	NS	-	-	-	-	-	-
epi- α -amyrin	NS	-	-	-	-	-	-
eriodictiol	NS	-	-	-	-	-	-
ethanol	NS	-	-	-	-	-	-
α-fenchene	NS	-	-	-	-	-	-
β-fenchene	NS	-	-	-	-	-	-
genkwanin-4'-methyl ether	NS	-	-	-	-	-	-
glycolic acid	NS	-	-	-	-	-	-
genkwanin	NS	-	-	-	-	-	-
hesperidin	NS	-	-	-	-	-	-
hispidulin	NS	-	-	-	-	-	-
hispiduloside	NS	-	-	-	-	-	-
humulene epoxide I	NS	-	-	-	-	-	-
humulene epoxide II	NS	-	-	-	-	-	-
5-hydroxy-4',7-dimethoxyflavone	NS	-	-	-	-	-	-
hydroxybenzoic acid-4- β -D-glucoside	NS	-	-	-	-	-	-
4-hydroxybenzoyl glucoside	NS	-	-	-	-	-	-
α-hydroxyhydrocaffeic acid	NS	-	-	-	-	-	-
2- β -hydroxyoleanolic acid	NS	-	-	-	-	-	-
3-β-hydroxyurea-12,20(30)-dien-17-on acid	NS	-	-	-	-	-	-
19- α -hydroxyursolic acid	NS	-	-	-	-	-	-
isobornyl acetate	NS	-	-	-	-	-	-
isobutyl acetate	NS	-	-	-	-	-	-
isorosmaricine	NS	-	-	-	-	-	-
labiatic acid	NS	-	-	-	-	-	-
ledene	NS	-	-	-	-	-	-
luteolin	NS	NS	-	-	-	-	-
luteolin-7-glucoside	NS	-	-	-	-	-	-
6-methoxy-genkwanin	NS	-	-	-	-	-	-
6-methoxy-luteolin	NS	-	-	-	-	-	-
6-methoxy-luteolin-7-glucoside	NS	-	-	-	-	-	-
6-methoxyluteolin-7-methyl ether	NS	-	-	-	-	-	-
methyl ether	NS	-	-	-	-	-	-
methyl eugenol	NS	-	-	-	-	-	-
N-methyl rosmaricine	NS	-	-	-	-	-	-
neo-chlorogenic acid	NS	-	-	-	-	-	-
nepetin	NS	-	-	-	-	-	-
nepetrin	NS	-	-	-	-	-	-
1-octen-3-ol	NS	-	-	-	-	-	-
picrosalvin	NS	-	-	-	-	-	-
rosmadiol	NS	-	-	-	-	-	-
rosmaricine	NS	-	-	-	-	-	-
rosmaridiphenol	NS	-	-	-	-	-	-
rosmarinol	NS	-	-	-	-	-	-
rosmariquinone	NS	-	-	-	-	-	-
salvigenin	NS	-	-	-	-	-	-
santene	NS	-	-	-	-	-	-
salicylic-acid-2-β-D-glucoside	NS	-	-	-	-	-	-
α –selinene	NS	-	-	-	-	-	-
sinensetin	NS	-	-	-	-	-	-
β-sitosterol	NS	-	-	-	-	-	-

Table 3. Chemical constituents by plant part [74]

Constituent*	Plant	Leaf	Flower	Shoot	Resin, Exudate, Sap	Essential Oil	Tissue Culture
squalene	NS	-	-	-	-	-	-
syringic-acid-4-β-D-glucoside	NS	-	-	-	-	-	-
tannin	NS	-	-	-	-	-	-
thymol	NS	-	-	-	-	-	-
trimethylalkane	NS	-	-	-	-	-	-
o-o-N-trimethylrosmaricine	NS	-	-	-	-	-	-
vanillic-acid-4-β-D-glucoside	NS	-	-	-	-	-	-
verbenol	NS	-	-	-	-	-	-
betulinic acid	-	NS	-	-	-	-	-
δ-4-carene	-	NS	-	-	-	-	-
diosmin	-	NS	-	-	-	-	-
7-ethoxy-rosmanol	-	NS	-	-	-	-	-
luteolin-3'-o-(3"-o-acetyl)- β -D-glucuronide	-	NS	-	-	-	-	-
luteolin-3'-o-(4"-o-acetyl)- β -D-glucuronide	-	NS	-	-	-	-	-
luteolin-3'-o- β -D-glucuronide	-	NS	-	-	-	-	-
monomethyl alkane	-	NS	-	-	-	-	-
pristane	-	NS	-	-	-	-	-
protocatechuic-acid-4-β-D-glucoside	-	NS	-	-	-	-	-
pectin	-	-	-	NS	-	-	-
acetic acid	-	-	-	-	NS	-	-
butan-2-ol	-	-	-	-	NS	-	-
caproic acid	-	-	-	-	NS	-	-
deca-trans-2,trans-4-dien-1-al	-	-	-	-	NS	-	-
hept-trans-2-en-1-al	-	-	-	-	NS	-	-
heptan-1-al	-	-	-	-	NS	-	-
heptan-2-ol	-	-	-	-	NS	-	-
heptanoic acid	-	-	-	-	NS	-	-
hexan-1-al	-	-	-	-	NS	-	-
hexan-1-ol	-	-	-	-	NS	-	-
3-methyl-butan-1-ol	-	-	-	-	NS	-	-
β-ocimene	-	-	-	-	NS	-	-
octan-1-ol	-	-	-	-	NS	-	-
octane-2,3-dione	-	-	-	-	NS	-	-
octanoic acid	-	-	-	-	NS	-	-
pentan-1-al	-	-	-	-	NS	-	-
pentan-1-ol	-	-	-	-	NS	-	-
pentan-2-ol	-	-	-	-	NS	-	-
zingiberene	-	-	-	-	NS	-	-
dipentene	-	-	-	-	-	NS	-

*constituents reported in ppm
NS – amount not specified
" – " means not reported

Table 4. Constituent data by plant part and chemical class

	Reference
Plant part not specified	
- volatile oil (0.5-2.5%): 1,8-cineole (15- 30%); camphor (15-25%); α-pinene (up to 25%); other monoterpenes (including borneol and limonene) - rosmarinic acid - diterpene bitter substances: carnosol; rosmanol; rosmadiol - triterpene acids: ursolic acid; oleanolic acids; rosmanol; 7-ethoxyrosmanol; betulic acid; carnosol; traces of 19 α-hydroxyursolic, 2 β-hydroxyoleanolic, and 3 β-hydroxyurea-12,20(30)-dien-17-oic acids - triterpene alcohols: α-amyrin; β-amyrin; betulin - flavonoids: luteolin; genkwanin (7-*O*-methlylapigenin); diosmetin; diosmin; genkwanin-4'-methyl ether; 6-methoxygenkwanin; 6-methyoxyluteolin; 6-methoxyluteolin-7-glucoside; 6-methoxyluteolin-7-methylether; hispidulin; apigenin - corresponding glycosides	3,6
Leaf	
- volatile oil (1.0-2.5%): 1,8-cineole (15-55%); camphor (5-25%); α-pinene (9-26%); camphene (2.5-12%); β-pinene (2-9%); borneol (1.5-6%); limonene (1.5-5%); bornyl acetate (1-5%); isobutyl acetate; β-caryophyllene; p-cymene; linalool; myrcene; α-terpineol (12-24%); verbenol - diterpenes (up to 4.6%): carnosic acid; carnosol; isorosmanol; rosmadiol; rosmaridiphenol; rosmanol; rosmariquinone; triacetylrosmanol; dimethylrosmanol - triterpenes: oleanolic acid (10%); ursolic acid (2-5%); α-amyrin; β-amyrin; epi-α-amyrin; 19-α-ursolic acid; 2-β-hydroxy oleanolic acid; betulin - phenolic acids (2-3%): rosmarinic acid (3.5%); chlorogenic acid; neo-chlorogenic acid; caffeic acid; labiatic acid - flavonoids: genkwanin; cirsimarin; diosmetin; apigenin; luteolin; nepetin; nepitrin; diosmin; hesperidin; homoplantiginin; phegopolin - alkaloids: rosmaricin; isorosmaricine - tannins - saponins - glycolic acid and glyceric acid - vitamin C; vitamin P - choline	27,39,40,53,75
Leaf Oil	
- α-pinene (8-25%), β-pinene (7.6%); eucalyptol (20-50%), camphor (10-27.6%), borneol (20%), 1,8-cineole (15.8%); β-myrcene (10%); camphene (5.2-5.8%), limonene (5.9%); *p*-cymene (4.8%); β-caryophyllene (3.1%); verbenone (2.6%); linalool	39,71,76-78
- From one sample (concentration in the oil): - monoterpenoid esters (24.76%): bornyl acetate (20.86%); linolyl acetate (2.90%); terpinyl acetate (1.0%) - monoterpenoid alcohols (23.78%): borneol (8.25%); linalool (5%); isoborneol (4.13%); γ-terpineol (2.94%); α-terpineol (1.9%); terpinene 4-ol (1.43%); carveol (0.13%) - monoterpenoid ketones (18.67%): L-camphor (14.06%); verbenone (2.56%); carvone (1.9%); α-thujone (0.15%) - monoterpenoid ethers (10.86%): methyl eugenol (5.46%); 1,8-cineole (5.05%); linalool oxide (0.35%) - sesquiterpenes (8.96%): β-caryophellene (4.31%); caryophellene oxide (3.19%); spathulenol (1.27%); α-copene (0.19%) - phenols (4.06%): thymole (3.06%); carvacrol (0.91%); methyl chavicol (0.19%) - monoterpenes (3.4%): p-cymene (1.15%); α-pinene (0.95%); camphene (0.81%); myrcene (0.22%); limonene (0.15%)	76
Essential Oil	
- mainly monoterpenes: α-pinene (20.1-21.7%), β-pinene; camphene; limonene; 1,8-cineole (23.5-26.5%); eucalyptol (4.5%); and borneol - camphor (7.2%); berbonone (7.6%); linalool; verbenol; terpineol; 3-octanone; isobornyl acetate	6,79,80

Table 5. Rosmarinus Officinalis (Rosemary) Leaf Extracts (CO_2 extract) – Certificates of Analysis

Analytical Detail	Specifications (%)	Results (%)
Rosmarinus Officinalis (Rosemary) Extract (CO_2) [22]		
Essential Oil Content	78-88	78
Volatile components:		
α-pinene	8-12	11.4
camphene	n.s.	4.0
β-pinene	n.s.	3.7
myrcene	n.s.	2.7
p-cymene	n.s.	1.2
limonene	2-4	2.4
1,8-cineole	>40	41.3
linalool	n.s.	0.83
camphor	6-13	13.0
borneol	n.s.	3.8
α-terpineol	n.s.	3.9
verbenone	n.s.	0.45
bornyl acetate	n.s.	0.94
carophyllene	3-10	4.7

Table 5. Rosmarinus Officinalis (Rosemary) Leaf Extracts (CO_2 extract) – Certificates of Analysis

Analytical Detail	Specifications (%)	Results (%)
Rosmarinus Officinalis (Rosemary) Leaf Extract (CO_2; 14% diterpene phenols) (and) Helianthus Annuus Seed Oil [23]		
Essential Oil Content	<2	1.9
Phenolic diterpenes:		
rosmanol	n.s.	0.07
7-methyl-rosmanol	n.s.	0.09
carnosol	n.s.	1.2
carnosolic acid	n.s.	10.5
12-methyl-carnosolic acid	n.s.	2.4
sum of phenolic diterpenes	13-15	14.3
Reference antioxidant compounds (carnesol + carnosic acid, calculated as carnosic acid)	n.s.	9.5
Ursolic Acid	n.s,	0.43
Oleanolic Acid	n.s.	0.62
residual ethanol	<2	0.71
water content	<1	0.30
Rosmarinus Officinalis (Rosemary) Leaf Extract (CO_2; 25% diterpene phenols) (and) Helianthus Annuus Seed Oil [24]		
Essential Oil Content	<4	3.0
Phenolic diterpenes:		
rosmanol	n.s.	0.13
7-methyl-rosmanol	n.s.	0.18
carnosol	n.s.	1.4
carnosolic acid	n.s.	18.7
12-methyl-carnosolic acid	n.s.	4.5
sum of phenolic diterpenes	24-26	24.9
Ursolic Acid	n.s.	0.29
Oleanolic Acid	n.s.	0.51
residual ethanol	<2	0.39
water content	<1	0.91
Rosmarinus Officinalis (Rosemary) Leaf Extract (CO_2; 25% diterpene phenols) (and) Helianthus Annuus Seed Oil [21]		
Essential Oil Content	<4	1.7
Phenolic diterpenes:		
rosmanol	n.s.	0.t3
7-methyl-rosmanol	n.s.	0.32
carnosol	n.s	2.9
carnosic acid	> t6	20.6
12-methyl-carnosic acid	n.s.	1.0
sum of phenolic diterpenes	24-26	25.0
Ursolic Acid	n.s.	0.42
Oleanolic Acid	n.s.	0.52
residual ethanol	<2	0.33
water content	<1	0.15

n.s. – not specified

Table 6. Differences in constituent profiles in Rosmarinus officinalis (rosemary) Leaf Extract based on extraction method *[12]

		Extraction Method				
Constituent (ppm)	**dried leaves**	**supercritical CO_2**	**acetone**	**ethanol extract, partially deodorized**	**ethanol extract, deodorized**	**decolorized and deodorized using hexane and ethanol**
Triterpenes						
betulin	<4760	6000	5600	8450	9460	6790
amyrin	<500	34	200	160	230	360
oleanic+ursolic acid	148,100	48,500	100,500	119,800	164,500	60,000
Flavonoids						
genkwanin	2.9	0.65	1.60	2.30	3.66	2.1
Volatiles						
1,8-cineole	56,100	80	1700	1320	53	30
camphor	25,200	220	2360	2080	120	20
borneol	10,000	90	960	840	40	10
Heavy Metals						
lead	2.90	0.09	0.03	0.13	0.15	0.18
arsenic	1.14	<0.034	0.05	0.25	0.25	0.32

* standardized to 10% carnosic acid + carnosol content

Table 7. Toxicity information on constituents of Rosmarinus officinalis (rosemary)

Component	Toxicity information
Phenol Acids	
Caffeic Acid	- in a MMC-induced SCE assay in human lymphocytes, 100 µM caffeic acid enhanced MMC-induced SCEs by 55%; 100 µM caffeic acid alone enhanced MMC-induced SCEs by 26%[81] - caffeic acid is reported to penetrate skin and have UV photoprotective activity[82] - humans and animals metabolize caffeic acid to the same metabolites and hydrolyze chlorogenic acid to caffeic acid; IARC concluded that there is sufficient evidence for carcinogenicity in animal; no data were available on the carcinogenicity in humans, and IARC concluded that caffeic acid is possibly carcinogenic to humans[83] - the carcinogenic potency of caffeic acid, estimated based on an average human intake of 1 mg/kg bw/day, was less than 1000 cancer cases per 1,000,000 individuals; in rats 1 or 2% (10,000 or 20,000 ppm) caffeic acid in the diet for 51 wks to 2 yrs induced papillomas of the forestomach and renal adenomas; one study, in which rats were exposed to 2% (20,000 ppm) caffeic acid in the diet for 2 yrs, showed treatment-induced carcinomas of the forestomach, whereas two studies with shorter exposure durations showed no such effect; caffeic acid was shown to exert strong promotion activity for forestomach carcinogenesis; chronic exposure to caffeic acid in the diet induced hyperplasia of the forestomach (mice, rats, and hamsters), hyperplasia of the kidney (mice and rats), and increased liver and kidney wts (rats); few toxic effects resulted from acute exposure; subchronic dietary exposures did not induce clinical symptoms of toxicity, however, hyperplasia of the forestomach was observed; some genotoxic effects seen in vitro but not in vivo[84]
Chlorogenic Acid	-an antioxidant that inhibited tumor promotion by phorbol esters in mice; some controversy exists over allergic reactions in green coffee beans, but it was accepted that chlorogenic acid was not the allergen[82] -in mice, 2% (20,000 ppm) chlorogenic acid in the diet for 96 weeks induced papillomas and carcinomas of the forestomach, alveolar type II-cell tumors of the lung, and renal cell adenomas; few toxic effects resulted from acute exposure; subchronic dietary exposures did not induce clinical symptoms of toxicity, however, reduced kidney and adrenal wts and hyperplasia of the forestomach were observed; some genotoxic effects seen in vitro but not in vivo[84]
Flavonoids	epidemiological studies implicated high dietary intake levels of flavonoids in heart disease, but a study of cancer risk failed to find a link; some evidence of genotoxicity in bacterial assays, but a European Organization of Cosmetic Ingredients Industries and Services (UNITIS) report stated that flavonoids do not appear to be genotoxic to mammals in vivo; flavonoids are not considered allergens[82]
Diterpenes	
Carnosic Acid	- is a known antioxidant;[85] in a toxicokinetic study in male Sprague-Dawley rats, carnosic acid was absorbed into the blood stream after oral administration and was bioavailable, traces of the acid were found in the intestinal content, liver, and muscle tissue of the abdomen and legs, carnosic acid was present in its free form, and the main rout of elimination was the feces;[85] not mutagenic in an Ames test, with or without metabolic activation, at doses equivalent of the concentration present in up to 6000 µg/plate of a decolorized and deodorized rosemary leaf extract[12]
Carnosol	- topical application of carnosol isolated from rosemary inhibited TPA-induced ear inflammation and tumor promotion in mice;[48] not mutagenic in an Ames test, with or without metabolic activation, at doses equivalent of the concentration present in up to 6000 µg/plate of a decolorized and deodorized rosemary leaf extract[12]
Monoterpenes	these chemicals may be skin irritants[82]
d- Limonene	- d-limonene consumption has been estimated as 0.2 -2 mg/kg bw/day; in men, oral intake induced transient proteinuria[83] - developmental toxicity in the form of delayed prenatal growth has been observed in mice, rats and rabbits exposed to *d*-limonene during gestation, and skeletal anomalies have also been observed in the fetuses of exposed mice and rabbits;[86] - the few genotoxicity studies available indicated that *d*-limonene and its 1,2-epoxide metabolite are not genotoxic[86] - in a mouse study, administration by gavage did not result in any treatment-related tumors; in a rat study, administration by gavage significantly increased the combined incidence of renal tubular adenomas and carcinomas and induced renal tubular hyperplasia in male rats, but no increases were seen in female rats;[86] oral treatment with *d*-limonene after administration of N-nitrosoethylhydroxyethylamine enhanced the development of renal adenomas and renal tubular hyperplasia in male Fischer 344 rats but not in male NBR rats;[83] - IARC found there are sufficient evidence for carcinogenicity in animals, concluding that *d*-limonene produces renal tubular tumors in male rats by a non-DNA-reactive mechanism, through an α_{2u}-globulin-associated response, and therefore, the mechanism by which *d*-limonene increases the incidence of renal tubular tumors in male rats is not relevant to humans; no data were available on the carcinogenicity in humans, and IARC concluded that d-limonene is not classifiable as to its carcinogenicity in humans[86]
α-Pinene	negative in the Ames assay and a mouse micronucleus test[87]
1,8-Cineole	positive in a sister chromatid exchange assay; negative in a chromosomal aberration assay; negative in an Ames test[88]
β-Myrcene	has been reported to cause dermatitis and conjunctivitis in humans; in Wistar rats, the NOAEL for embryotoxicity was 0.5 g/kg bw/day and the NOAEL for peri- and post-natal developmental toxicity was 0.25 g/kg bw/day; was not genotoxic *in vitro* in SCE and chromosomal aberration assays in Chinese hamster cells or human lymphocytes, but it did induce a slight increase is SCEs in cultured hepatic tumor cells; was not genotoxic *in vivo* in rat bone marrow cells[89]
Linalool	safe at up to 4.3% (20% in consumer fragrance); listed as a fragrance allergen by the European Commission[82]
α,β-Thujone	α,β-thujone was not mutagenic in the Ames test; in the micronucleus test, negative in male and positive in female mice; β-thujone: *some evidence of carcinogenicity in male rats* – significant incidence of cancers of the preputial gland in male rats given 25 mg/kg by gavage, and an increase in adrenal gland tumors in male rats may have been due to β-thujone; no increase in in cancer incidence in female rats (dosed with up to 50 mg/kg by gavage) or male or female mice (dosed with up to 25 mg/kg by gavage); all rats dosed with 50 mg/kg and all female mice dosed with 25 mg/kg died[90]
Methyleugenol	- IARC concluded that there is sufficient evidence in experimental animals for carcinogenicity; no data were available on the carcinogenicity in humans, and IARC concluded that methyleugenol is possibly carcinogenic to humans[91]

Table 7. Toxicity information on constituents of Rosmarinus officinalis (rosemary)

Component	Toxicity information
Terpene Alcohols	
α-Terpineol	- oral LD50 in mice, 2830 mg/kg; 1000 mg/kg bw/day for 2 wks caused reduced body wt gains and an increase in serum cholesterol; not mutagenic in an Ames test or mouse lymphoma assay; did not induce pulmonary tumors in mice given i.p. injections; a derma irritant in animals studies, but not a dermal irritant in a 4-h clinical study; not a sensitizer in guinea pigs; in clinical patch tests, 5% in pet. had 1/1606 positive and 11/1606 questionable reactions in one study and 2/1200 positive reactions in another[92]
Ursolic acid	topical application of carnosol isolated from rosemary inhibited TPA-induced ear inflammation and tumor promotion in mice[48]
Triterpene Alcohols	hepatoprotective and anti-carcinogenic activity has been suggested for lupeol; no toxicity data were available; triterpene alcohols were considered to have intermediate risk[82]

Table 8. Frequency and concentration of use according to duration and type of exposure

	# of Uses[30]	*Max. Conc. of Use (%)*[31]	*# of Uses*[30]	*Max. Conc. of Use (%)*[31]	*# of Uses*[30]	*Max. Conc. of Use (%)*[31]
	Rosmarinus Officinalis (Rosemary) Extract		**Rosmarinus Officinalis (Rosemary) Flower Extract**		**Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Extract**	
Totals*	**387**	**0.00004-0.16**	**36**	**NR**	**NR**	**0.0024**
Duration of Use						
Leave-On	*234*	*0.00096 – 0.051*	*11*	*NR*	*NR*	*0.0024*
Rinse Off	*150*	*0.00004 -0.16*	*25*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*3*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	18	0.01-0.05	2	NR	NR	NR
Incidental Ingestion	7	0.011	NR	NR	NR	NR
Incidental Inhalation-Spray	6[a]	0.00096-0.01[a]	1	NR	NR	NR
Incidental Inhalation-Powder	NR	0.05	NR	NR	NR	NR
Dermal Contact	265	0.00096-0.16	11	NR	NR	0.0024
Deodorant (underarm)	NR	not spray: 0.0098 aerosol: 0.0098-0.012	NR	NR	NR	0.0024
Hair - Non-Coloring	112	0.00004-0.003	25	NR	NR	NR
Hair-Coloring	1	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	27	0.0005-0.16	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Rosmarinus Officinalis (Rosemary) Leaf		**Rosmarinus Officinalis (Rosemary) Leaf Extract**		**Rosmarinus Officinalis (Rosemary) Leaf Oil**	
Totals*	**16**	**0.002**	**689**	**0.00001-10**	**516**	**0.00001-1.5**
Duration of Use						
Leave-On	*1*	*0.002*	*422*	*0.00001-10*	*342*	*0.0003-1.5*
Rinse Off	*14*	*NR*	*263*	*0.00001-3*	*149*	*0.00001-0.12*
Diluted for (Bath) Use	*1*	*NR*	*4*	*0.0002-0.04*	*25*	*0.5-0.97*
Exposure Type						
Eye Area	NR	NR	36	0.002-3	8	*NA*
Incidental Ingestion	NR	NR	25	0.00001-0.002	3	0.008
Incidental Inhalation-Spray	NR	NR	9[a]	0.001-0.5 aerosol: 0.0016 pump spray: 0.0001-0.005	32	0.011-1.5 aerosol: 0.007
Incidental Inhalation-Powder	NR	NR	8	0.0002	3	0.0003
Dermal Contact	4	NR	416	0.00001-10	425	0.0003-1.5
Deodorant (underarm)	NR	NR	NR	NR	1	NA
Hair - Non-Coloring	12	0.002	225	0.00001-0.5	87	0.00001-1.5
Hair-Coloring	NR	NR	22	0.04	1	NA
Nail	NR	NR	1	0.005-0.053	NR	NA
Mucous Membrane	1	NR	74	0.00001-3	66	0.002-0.97
Baby Products	NR	NR	7	0.012	4	NA

Table 8. Frequency and concentration of use according to duration and type of exposure

	# of Uses[30]	*Max. Conc. of Use (%)*[31]	*# of Uses*[30]	*Max. Conc. of Use (%)*[31]	*# of Uses*[30]	*Max. Conc. of Use (%)*[31]
	Rosmarinus Officinalis (Rosemary) Leaf Powder		**Rosmarinus Officinalis (Rosemary) Leaf Water**		**Rosmarinus Officinalis (Rosemary) Water**	
Totals*	**1**	**0.05**	**22**	**0.000069-1**	**1**	**---**
Duration of Use						
Leave-On	*1*	*NR*	*7*	*0.000069-1*	*1*	*NR*
Rinse Off	*NR*	*0.05*	*15*	*0.00015-0.25*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	0.000069-0.00016	NR	NR
Incidental Ingestion	NR	NR	NR	0.005	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	1	NR	7	0.00009-0.36	1	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.05	15	0.00019-1	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	0.005	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Rosemary [#]					
Totals*	**12**	**---**				
Duration of Use						
Leave-On	*4*	---				
Rinse Off	*7*	---				
Diluted for (Bath) Use	*1*	---				
Exposure Type						
Eye Area	NR	---				
Incidental Ingestion	NR	---				
Incidental Inhalation-Spray	NR	---				
Incidental Inhalation-Powder	1	---				
Dermal Contact	8	---				
Deodorant (underarm)	NR	---				
Hair - Non-Coloring	4	---				
Hair-Coloring	NR	---				
Nail	NR	---				
Mucous Membrane	2	---				
Baby Products	NR	---				

* Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types my not equal the sum of total uses
NR – not reported
[a] Includes suntan preparations, and it t is not known whether or not those product are sprays
[#]Genus, species, plant part, and method of extraction not known

Table 9. Single-dose toxicity studies

Test Article	Extraction Solvent/Method	Species	No./Group	Vehicle	Conc/Dose Range	LD_{50}/Results	Reference
			DERMAL				
Rosmarinus Officinalis (Rosemary) Leaf Oil	-----	rabbits	not stated	not stated	not stated	>10 ml/kg	59
Rosmarinus Officinalis (Rosemary) Leaf Oil	-----	rabbits	not stated	not stated	not stated	>10 g/kg	77
			ORAL				
Rosmarinus Officinalis (Rosemary) Leaves – 2 samples; one harvested in autumn (112.7, 477.8, 700.1 µg/mg extract carnosol, carnosic acid, total diterpenes, respectively) and one in spring (45.9, 245.9, 343.1 µg/mg ex tract carnosol, carnosic acid, total diterpenes, respectively)	supercritical CO_2	Wistar rats	6 M/6F	corn oil	2 g/kg bw (gavage)	>2 g/kg	27
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	ethanol extract, partially deodorized	mice	not stated	none stated	8.5 g/kg bw (males) 10 g/kg bw (females)	>8.5 g/kg bw (males) >10 g/kg bw (females)	12
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	ethanol extract, deodorized	mice	not stated	none stated	24 g/kg bw (males) 28.5 g/kg bw (females)	>24 g/kg bw (males) >28.5 g/kg bw (females)	12
Rosmarinus Officinalis (Rosemary) Leaf Oil (see Table 4 for composition)	hydrodistillation	Swiss albino rats	20/group	-----	2-9 g/kg bw (gavage)	LD_{50} = 5.50 g/kg bw LD_{10} = 1.10 g/kg bw LD_{100} = 9 g/kg bw	76
Rosmarinus Officinalis (Rosemary) Leaf Oil (see Table 5 for composition)	-----	rats	not stated	none stated	not stated	5 ml/kg bw	59
			PARENTERAL				
Rosmarinic Acid	-----	mice	not stated	none stated	not stated	561 mg/kg (i.v.)	93

Table 10. Repeated-Dose Toxicity Studies

Test Article	Extraction Solvent/Method	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Results	Reference
				ORAL			
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	ethanol extract, partially deodorized	mice; no./group not stated	5 days (gavage)	none stated	4300 mg/kg bw (males) 5000 mg/kg bw (females)	- no mortality - body wt increased slightly in males, but no changes were seen in females; "marked increase" in fatty liver was observed in males after repeated administration	12
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table for composition)	ethanol extract, deodorized	mice; no./group not stated	5 days (gavage)	none stated	11,800 mg/kg bw (males) 14,100 mg/kg bw (females)	- no changes in body wts; liver wts of females were slightly increased; fatty livers were observed in test animals at necropsy.	12
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	acetone	rats; no./group not stated	14 day (diet)	-----	up to 3800 mg/kg diet	- no treatment-related signs of toxicity, mortality, or changes in body wts or feed consumption	12
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	supercritical CO_2	rats; no./group not stated	14 days (diet)	-----	up to 2400 mg/kg diet	- no treatment-related signs of toxicity, mortality, or changes in body wts or feed consumption	12
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	acetone	20 rats/group	13 wks (diet)	-----	300, 600, 2400, or 3800 mg/kg diet	- variations in clinical chemistry parameters at times were stat sig, but the researchers stated that because the changes were inconsistent, they were not considered dose-related - stat. sig, decrease in alkaline phosphate in the 3800 mg/kg group - NOAEL was 3800 mg/kg diet	12
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	supercritical CO_2	20 rats/group	13 wks (diet)	-----	300, 600, or 2400 mg/kg diet	- variations in clinical chemistry parameters at times were stat sig; the researchers stated that because the changes were inconsistent, they were not considered dose-related - a marginal reduction in body weights and feed consumption in the animals of the 2400 mg/kg diet groups were attributed to a lack of palatability of the feed - changes were more notable in females - NOAEL was 2400 mg/kg diet (equiv. to 180 and 200 mg/kg bw/day form males and females, respectively)	12
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	supercritical CO_2	female rats; no./ group not stated	91 days (diet); 28-day recovery period	-----	0 or 2400 mg/kg diet (equiv. to 0 or 195 mg/kg bw/day)	- slight increase in liver wts after 91-days of dosing, but not in those killed after the 28-day recovery period - an increase in microsomal protein concentration observed after 91 days of dosing was also reversible - no notable effects on the activity of selected enzymes	12
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	ethanol extract, partially deodorized	Sprague-Dawley rats; no./group not stated	90 days (diet)	-----	0, 500, 1500,or 5000 mg/ kg diet (equiv. to 0, 40, 120, or 400 mg/kg bw/day)	- a dose-response relationship was observed for relative liver-to-body wt; extracts; a slight but stat sig increase was observed - no microscopic changes in the liver were reported	12
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	ethanol extract, deodorized	Sprague-Dawley rats; no./group not stated	90 days (diet)	-----	0, 500, 1500,or 5000 mg/ kg diet (equiv. to 0, 40, 120, or 400 mg/kg bw/day)	- a dose-response relationship was observed for relative liver-to-body wt; extracts; a slight but stat sig increase was observed - no microscopic changes in the liver were reported	12

Table 10. Repeated-Dose Toxicity Studies

Test Article	Extraction Solvent/Method	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Results	Reference
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	hexane and ethanol (2-step extraction)	Sprague-Dawley rats; no./group not stated	3 mos (diet); 28-day interim group; 1-mo recovery period	-----	0, 1000, 2500, or 5000 mg/kg diet (equiv. to 0, 65, 164, or 320 mg/kg bw/day)	- no signs of toxicity, no mortality and no gross lesions at necropsy - reversible dose-dependent increases in absolute liver wts and relative liver-to-body wts; stat sig in the high dose group only - treatment-related increase in bile duct hyperplasia at the interim necropsy; the incidence was decreased at the end of dosing and not seen after recovery - in females, a decrease in pancreas wt was observed at the interim necropsy - no stat sig changes in hematology parameters, and no microscopic changes - the NOAEL was at least 320 mg/kg bw/day	12
Rosmarinus Officinalis (Rosemary) Leaf Extract (after the volatile oil [1.1%] was removed)	absolute ethanol	Swiss albino mice; 6M/group	3 wks (gavage)	olive oil	1500 mg/kg extract controls – olive oil	no stat sig changes in relative liver, spleen, heart, or lung wt to body wt compared to controls; there were no stat sig changes in clinical chemistry parameters	76
			single dose CCl_4 (gavage), then 3 wks extract (gavage)	olive oil	3.3% CCl_4 (100 mg/kg bw) 1500 mg/kg extract	- with CCl_4 only, stat sig increases in relative liver to body wt (18%) and spleen to body wt (45.6%) compared to olive oil controls; CCl_4 affected all measured clinical chemistry parameters - with the extract, the increase in relative spleen to body wt was stat sig, but not as great as with CCl_4 alone (34.9%); there was no stat sig increase in relative liver to body wt; many of the changes in clinical chemistry values were reduced or were non-stat sig	
Rosmarinus Officinalis (Rosemary) Leaf Oil (see Table 4 for composition)	hydrodistillation	Swiss albino mice; 6M/group	3 wks (gavage)	-----	1100 mg/kg bw controls – olive oil	no stat sig changes in relative liver, spleen, heart, or lung wt to body wt compared to controls; there were no stat sig changes in clinical chemistry parameters	76
			single dose CCl_4 (gavage), then 3 wks oil (gavage)	olive oil (for CCl_4)	3.3% CCl_4 (100 mg/kg bw) 1100 mg/kg extract	- (effects of CCl_4 only are described above) - with the oil, the increases in relative liver to body wt (9.8%) and spleen to body wt (38.8%) were stat sig, but not as great as with CCl_4 alone; many of the changes in clinical chemistry values were reduced but were still stat sig	
Rosmarinic Acid	-----	C57BL/6J Min/+ (*Apc*^{Min}) mice; 6-7M and 6-7F/grp	8 wks	-----	0 or 0.3% in feed	- no signs of toxicity, no effect on weight gains	94

Abbreviations: CCl_4: - carbon tetrachloride; conc – concentration; equiv. – equivalent; NOAEL – no-observable adverse effect level; stat sig – statistically significant

Table 11. Genotoxicity studies

Test Article	Extraction Solvent/Method	Conc./Vehicle	Procedure	Test System	Results	Reference
			IN VITRO			
Rosemary Extract (not defined; water-soluble; contained 17% rosmarinic acid)	-----	50, 100, or 200 µg/plate	Ames test, with and without metabolic activation	*S. typhimurium* TA98	not mutagenic	95
as above	-----	50 µg/ml (highest non-cytotoxic dose)	comet assay	human hepatoma cell line (HepG2)	not genotoxic	95
Rosemary Extract (not defined; oil-soluble; contained 50.27% carnosic acid and 5.65% carnosol)	-----	50, 100, or 200 µg/plate	Ames test, with and without metabolic activation	*S. typhimurium* TA98	not mutagenic	95
as above	-----	5 µg/ml (highest non-cytotoxic dose)	comet assay	human hepatoma cell line (HepG2)	not genotoxic	95
Rosmarinus Officinalis (Rosemary) Leaf Extract	supercritical CO_2	up to 5000 µg/plate	bacterial assay, with and without metabolic activation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA102	not mutagenic - in TA102 only, toxicity at the highest dose with metabolic activation	12
Rosmarinus Officinalis (Rosemary) Leaf Extract	ethanol extract,, partially deodorized	up to 20,000 µg/plate	bacterial assay, with and without metabolic activation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA102	not mutagenic - some bactericidal effects in all strains; effects were reduced with metabolic activation	12
Rosmarinus Officinalis (Rosemary) Leaf Extract	ethanol extract, deodorized	up to 20,000 µg/plate	bacterial assay, with and without metabolic activation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA102	not mutagenic - some bactericidal effects in all strains; effects were reduced with metabolic activation	12
Rosmarinus Officinalis (Rosemary) Leaf Extract	hexane and ethanol (2-step extraction)	up to 6000 µg/plate	Ames test, with and without metabolic activation	*S. typhimurium* TA97, TA98, TA100, TA102	-mutagenic in TA102 in one set of trials; not reproducible with less cytotoxic conc -not mutagenic in the other strains - without metabolic activation: bactericidal for all strains at 3000-6000 µg/plate; bactericidal to TA102 at almost all dose levels -with metabolic activation, bactericidal only at the highest dose level, if at all	12
Rosmarinus Officinalis (Rosemary) Leaf Extract	ethanol extract, partially deodorized	up to 100 mg/ml	chromosomal aberration assay, with and without metabolic activation	human lymphocytes	not genotoxic	12
Rosmarinus Officinalis (Rosemary) Leaf Extract	hexane and ethanol (2-step extraction)	not clearly specified but at least up to 50 µg/ml without and 35 µg/ml with metabolic activation	gene-locus mutation assay, with and without metabolic activation	thymidine kinase (tk) and hgprt loci of a human lymphoblastoid cell line (TK6)	-not genotoxic without metabolic activation at up to 50 µg/ml - 35 µg/ml increased mutations in the tk, but not the hgprt, locus with activation; the increase was stat sig when compared to solvent control, but not when compared to untreated cells; determined to be not mutagenic under the conditions used because of a lack of a dose-dependent increase in mutation frequency and a lack of a stat sig increase of mutation frequency compared to controls	12
Rosmarinus Officinalis (Rosemary) Leaf Oil	-----	not stated	Ames test	not stated	negative	96
Rosmarinic Acid	-----	0, 0.28, 0.56, or 1.12 mM in distilled water	cytokinesis-block micronucleus test; 0.5 µg/ml doxorubicin was used as the positive control	Chinese hamster lung fibroblasts (V79 cells)	not genotoxic; no stat sig increase in the induction of micronuclei	9

Table 11. Genotoxicity studies

Test Article	Extraction Solvent/Method	Conc./Vehicle	Procedure	Test System	Results	Reference
Rosmarinic Acid	-----	0, 0.28, 0.56, or 1.12 mM in distilled water	comet assay; 0.5 µg/ml doxorubicin was used as the positive control	Chinese hamster lung fibroblasts (V79 cells)	not genotoxic; no stat sig increase in the induction of DNA damage	9
			IN VIVO			
Rosmarinus Officinalis	hydro-alcoholic	6.43, 100, and 200 mg/kg bw	chromosomal aberration assay	Wistar rats; 6/group	not genotoxic	97
Rosmarinus Officinalis	hydro-alcoholic	6.43, 100, and 200 mg/kg bw	micronucleus assay	Wistar rats; 6/group	not genotoxic	97
Rosmarinus Officinalis (Rosemary) Leaf Extract (after the volatile oil [1.1%] was removed)	absolute ethanol	1500 mg/kg bw/day in olive oil	micronucleus test; dosed by gavage for 7 days; negative controls were given olive oil; positive controls were given a single i.p. dose of 100 mg/kg bw CPA; bone marrow cells collected 24 h after dosing	Swiss albino mice	not genotoxic; no stat sig change in the number of MNPCE or NCE or in PCE/NCE	76
Rosmarinus Officinalis (Rosemary) Leaf Oil (see Table 4 for composition)	hydrodistillation	1100 mg/kg bw/day	same protocol	Swiss albino mice	no stat sig change in no. of MNPCE no. of NCE was stat sig decreased ($p<0.05$) PCE/NCE was stat sig increased ($p<0.01$)	76
Rosmarinus Officinalis (Rosemary) Leaf Oil	hydrodistillation	300, 1000, or 2000 mg/kg bw (by gavage)	chromosome aberration assay; single 0.5 ml dose; negative controls were given distilled water; positive controls were dosed with 50 mg CPA/kg; bone marrow cells collected 24 h after dosing	Wistar rats; 3M/3F per group	- chromosomal aberrations without gaps were stat sig increased at 2000 mg/kg bw - mitotic index was stat sig increased with 300 mg/kg, but not with other doses or the positive control	18
Rosmarinus Officinalis (Rosemary) Leaf Oil	hydrodistillation	300, 1000, or 2000 mg/kg bw (by gavage)	micronucleus test; single 0.5 ml dose; negative controls were given distilled water; positive controls were dosed with 50 mg CPA/kg; bone marrow cells collected 24 h after dosing	Swiss mice; 3M/3F per group	- stat sig increase in MNPCEs with 1000 and 2000 mg/kg bw - PCE/NCE was not stat sig different from controls	18
Rosmarinus Officinalis (Rosemary) Leaf Oil	hydrodistillation	300, 1000, or 2000 mg/kg bw (by gavage)	micronucleus test; protocol as above; bone marrow cells collected 24 h after dosing	Wistar rats; 3M/3F per group	stat sig increase in MNPCEs with 2000 mg/kg bw	18
Rosmarinus Officinalis (Rosemary) Leaf Oil	hydrodistillation	300, 1000, or 2000 mg/kg bw (by gavage)	comet assay; single 0.5 ml dose; negative controls were given distilled water; positive controls were dosed with 50 mg cyclophosphamide/kg; liver and peripheral blood cells collected 24 h after dosing	Swiss mice; 3M/3F per group	all 3 doses induced stat sig increases in DNA damage in peripheral blood cells and liver cells; most of the damaged cells showed minor damage, very few had a large amount of damage	18
Rosmarinic Acid	hydrodistillation	50, 100, and 200 mg/kg bw in distilled water (by gavage)	micronucleus test; single 16.7 ml/kg bw; positive controls were dosed with 15 mg/kg bw doxorubicin; blood samples were taken 24, 48, and 72 h after dosing	male Swiss mice; 6/group	not genotoxic	98
Rosmarinic Acid	-----	0, 2, or 8 mg/kg in saline (i.p.)	comet assay; brain and peripheral blood cells collected after 3 h; MMS was used as the positive control	male Wistar rats	no stat sig increase in DNA damage when compared to the negative controls	10

Table 11. Genotoxicity studies

Test Article	Extraction Solvent/Method	Conc./Vehicle	Procedure	Test System	Results	Reference
mixture containing 19% Rosmarinus officinalis (rosemary) leaves, 71..5% St. John's Wort; 9.5% spirulina (algae)	-----	0, 380, 760, or 1520 mg/ kg bw/day in water (gavage)	micronucleus test; mice were dosed for 7 days; femoral bone marrow cells were used	male Swiss albino mice; 30/group	- stat. sig. increase in MNPCEs with 760 and 1520 mg/kg bw/day - PCE/NCE was not stat sig different from controls	99
mixture defined above	-----	0, 380, 760, or 1520 mg/ kg bw/day in water (gavage)	chromosomal aberration assay; mice were dosed for 7 days and killed 19 days after last dose	male Swiss albino mice; 30/group	- stat sig increased in frequency of aneuploidy with 760 and 1520 mg/kg bw/day - % polyploids and total % aberrations were stat sig increased at these doses	99
mixture defined above	-----	0, 380, 760, or 1520 mg/ kg bw/day in water (gavage)	assay for spermatozoa abnormality; mice were dosed for 7 days and killed 5 wks after last dose	male Swiss albino mice; 30/group	- stat sig increase in frequency of banana-shaped, swollen achrosome, and triangular head sperm abnormalities with 1520 mg/kg bw/day - % total spermatozoa abnormalities stat sig increased with 1520 mg/kg bw/day	99
ANTI-MUTAGENIC EFFECTS						
IN VITRO						
Rosemary Extract (not defined; contained 8.8-10.6% carnosic acid and 1.2-1.4% carnosol) + tBOOH	-----	≤0.8 mg/ml in medium-chain triglycerides; only the carnosic acid and carnosol were soluble	Ames test; 0.5 ml rosemary extract was incubated with 0.5 ml tBOOH	*S. typhimurium* TA102	stat sig reduced tBOOH-induced mutagenicity	100
Rosemary Extract (not defined; water-soluble; contained 17% rosmarinic acid) + IQ	-----	50, 100, or 200 µg/ plate extract 10 ng/plate IQ	Ames test, with metabolic activation	*S. typhimurium* TA98	a stat sig reduction in IQ-induced genotoxicity was observed only at the highest dose	95
as above + NQNO	-----	0, 50, 100, or 200 µg/ plate extract 500 ng/plate NQNO	Ames test, without metabolic activation	*S. typhimurium* TA98	no stat sig effect on NQNO-induced genotoxicity	95
as above + tBOOH	-----	0, 0.05, 0.5, 5, or 50 µg/ml extract; 0.05 mM tBOOH	Comet assay; pretreatment with extract for 21 h, followed by 20 min exposure to tBOOH	human hepatoma cell line (HepG2)	stat sig reduction in tBOOH-induced DNA damage at all doses; the reduction was not dose-dependent – 0.05 µg/ml caused a greater reduction than 0.5 µg/ml	95
as above + tBOOH	-----	0, 0.05, 0.5, 5, or 50 µg/ml extract; 0.05 mM tBOOH	Comet assay; co-treatment with extract and tBOOH for 20 min	human hepatoma cell line (HepG2)	no stat sig effect on tBOOH-induced DNA damage	95
as above + tBOOH	-----	0, 0.05, 0.5, 5, or 50 µg/ml extract; 0.05 mM tBOOH	Comet assay; pretreatment with extract for 21 h, followed by co-treatment with extract and tBOOH for 20 min	human hepatoma cell line (HepG2)	stat sig reduction in tBOOH-induced DNA damage at all except the lowest dose	95
as above + BaP	-----	0, 0.05, 0.5, 5, or 50 µg/ml extract; 40 µM BaP	by co-treatment with extract and BaP for 21 h	human hepatoma cell line (HepG2)	stat sig reduction in BaP-induced DNA damage only at the highest dose	95
as above + PhIP	-----	0, 0.05, 0.5, 5, or 50 µg/ml extract; 80 µM PhIP	Comet assay; by co-treatment with extract and PhIP for 21 h	human hepatoma cell line (HepG2)	stat sig reduction in PhIP-induced DNA damage only at the highest dose	95

Table 11. Genotoxicity studies

Test Article	Extraction Solvent/Method	Conc./Vehicle	Procedure	Test System	Results	Reference
Rosemary Extract (not defined; oil-soluble; contained 50.27% carnosic acid and 5.65% carnosol) + IQ	-----	50, 100, or 200 µg/ plate extract 10 ng/plate IQ	Ames test, with metabolic activation	*S. typhimurium* TA98	suppressed IQ-induced mutations in a stat sig, dose-dependent, manner	95
as above + NQNO	-----	50, 100, or 200 µg/ plate extract 500 ng/plate NQNO	Ames test, without metabolic activation	*S. typhimurium* TA98	suppressed NQNO-induced mutations in a stat sig, dose-dependent, manner	95
as above + tBOOH	-----	0, 0.05, 0.5, or 5 µg/ ml extract; 0.05 mM tBOOH	comet assay; pretreatment with extract for 21 h, followed by 20 min exposure to tBOOH	human hepatoma cell line (HepG2)	stat sig reduction in tBOOH-induced DNA damage at all doses	95
as above + tBOOH	-----	0, 0.05, 0.5, or 5 µg/ ml extract; 0.05 mM tBOOH	comet assay; co-treatment with extract and tBOOH for 20 min	human hepatoma cell line (HepG2)	no stat sig effect on tBOOH-induced DNA damage	95
as above + tBOOH	-----	0, 0.05, 0.5, or 5 µg/ ml extract; 0.05 mM tBOOH	comet assay; pretreatment with extract for 21 h, followed by co-treatment with extract and tBOOH for 20 min	human hepatoma cell line (HepG2)	stat sig reduction in tBOOH-induced DNA damage at all doses; the reduction was not dose-dependent`	95
as above + BaP	-----	0, 0.05, 0.5, or 5 µg/ ml extract; 40 µM BaP	by co-treatment with extract and BaP for 21 h	human hepatoma cell line (HepG2)	stat sig reduction in BaP-induced DNA damage at the two highest doses	95
as above + PhIP	-----	0, 0.05, 0.5, or 5 µg/ ml extract; 80 µM PhIP	by co-treatment with extract and PhIP for 21 h	human hepatoma cell line (HepG2)	stat sig reduction in PhIP-induced DNA damage at the two highest doses	95
Rosmarinic Acid + doxorubicin	-----	0, 0.28, 0.56, or 1.12 mM rosmarinic acid in distilled water; 5 µg/ ml doxorubicin	cytokinesis-block micronucleus test	Chinese hamster lung fibroblasts (V79 cells)	stat sig reduction in the frequency of doxorubicin-induced micronuclei when compared to the group given doxorubicin only	9
Rosmarinic Acid + doxorubicin	-----	0, 0.28, 0.56, or 1.12 mM rosmarinic acid in distilled water; 5 µg/ ml doxorubicin	comet assay	Chinese hamster lung fibroblasts (V79 cells)	stat sig reduction in the frequency of doxorubicin-induced DNA damage when compared to the group given doxorubicin only; the reduction was not dose-dependent	9
			IN VIVO			
Rosmarinus Officinalis (Rosemary) Leaf Extract (after the volatile oil [1.1%] was removed) + CPA	absolute ethanol	1500 mg/kg bw/day in olive oil	micronucleus test; dosed by gavage with the extract for 7 days, then given a single i.p. dose of 100 mg/kg bw CPA; bone marrow cells collected 24 h after dosing; olive oil was used as a negative control	Swiss albino mice	stat sig increase in the number of MNPCE and NCE compared to olive oil only; no stat sig change in PCE/NCE	76
Rosmarinus Officinalis (Rosemary) Leaf Oil (contained 20.86% bornyl acetate; 16.24% L-camphor, and 8.25% borneol) + CPA	hydrodistillation	1100 mg/kg bw/day	micronucleus test; dosed by gavage with the oil for 7 days, then given a single i.p. dose of 100 mg/kg bw CPA; bone marrow cells collected 24 h after dosing; olive oil was used as a negative control	Swiss albino mice	stat sig increase in the number of MNPCE and NCE, and a stat sig decrease in PCE/NCE, compared to olive oil only	76
Rosmarinic Acid + doxorubicin	-----	50, 100, and 200 mg/ kg bw rosmarinic acid in distilled water (by gavage); 15 mg/kg bw doxorubicin, i.p.	micronucleus test; single 16.7 ml/ kg bw rosmarinic acid + 10 ml/kg bw doxorubicin after 10 min; blood samples were taken 24, 48, and 72 h after dosing	male Swiss mice; 6/group	stat sig reduction in the frequency of doxorubicin-induced MNPCEs when compared to the group given doxorubicin only; the reduction was not dose-dependent	98

Abbreviations: BaP – benzo(*a*)pyrene; conc – concentration; CPA - cyclophosphamide: IQ – 2-amino-3-methyl-3H-imidao[4,5-F]quinoline; MMS – methyl methanesulfonate; MNPCE – micronucleated polychromatic erythrocytes; NCE – normochromatic erythrocytes; NQNO – 4-nitroquinoline-N-oxide; PCE/NCE – ratio of polychromatic erythrocytes to normochromatic erythrocytes; PhIP – 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; stat sig – statistically significant; tBOOH - t-butyl hydroperoxide

Table 12. Anti-tumor activity

Test Article	Extraction Solvent/Method	Dose/Exposure Route	Species No./Group	Tumor Type	Carcinogenicity Model	Results	Reference
Rosmarinus Officinalis (Rosemary) Leaf Extract (contained 16.5-19.2% urosolic acid; 3.8-4.6% carnosol; 0.1-0.5% carnosic acid; trace-0.1% miltirone)	methanol	1.2 or 3.6 mg; dermal	CD-1 mice; 30F/grp	skin	- initiation: topical treatment with 200 nmol DMBA in 200 µl acetone - promotion: after 1 wk, topical treatment with 200 µl acetone (controls), 5 nmol TPA in 200 µl acetone (carc grp), or 5 nmol TPA and extract in 200 µl acetone (RE grp), 2x/wk, for 20 wks	1.2 mg: decreased tumor/mouse by 48, 27, and 28% after 7, 11, and 15 wks TPA promotion 3.6 mg: decreased tumor/mouse by 84, 37, and 48% after 7, 11, and 15 wks TPA promotion	48
as above	methanol	1.2 or 3.6 mg; 5 min prior to B(a)P; dermal	CD-1 mice; 30F/grp	skin	- initiation: topical treatment with 200 µl acetone (controls) or with extract in 200 µl acetone (RE grp) 5 min prior to each 20 nmol application of B(a)P or 2 nmol DMBA, 1x/wk, for 10 wks - promotion: after 1 wk, promotion with 15 nmol TPA in 200 µl acetone, 2x/wk, for 20 wks	1.2 mg: decreased tumor/mouse by 15, 42, and 54% after 9, 13, or 21 wks TPA promotion 3.6 mg: decreased tumor/mouse by 62, 63, and 64% after 9, 13, or 21 wks TPA promotion	48
as above	methanol	3.6 mg; dermal	CD-1 mice; 30F/grp	skin	- initiation: topical treatment with 200 µl acetone (controls) or 3.6 mg extract in 200 µl acetone (RE grp) at 120, 60, and 5 min before topical application of 200 nmol B(a)P in 200 µl acetone - promotion: after 1 wk, 15 nmol in 200 µl acetone, 2x/wk, for 20 wks	decreased tumor/mouse by 83, 81, and 58% after 9, 13, or 21 wks TPA promotion	48
Rosmarinus Officinalis (Rosemary) Leaf Extract	DDW	500 mg/kg bw; gavage	Swiss albino mice; 12M/grp	skin	DMBA-initiated and croton oil-promoted skin tumorigenesis Grp 1: controls – topical treatment with 100 µl acetone; DDW by gavage for 15 wks Grp 2: 500 mg/kg bw/day RE in 100 µl DDW for 15 wks Grp 3: single topical dose 100 µg DMBA in 100 µl acetone; 2 wks later, 1% croton oil in acetone, 3 x/wk; also, 100 µl by gavage for 15 wks Grp 4: single topical dose 100 µg DMBA in 100 µl acetone; 500 mg/kg bw RE by gavage 7 days before, during, and 7 days after DMBA; 2 wks after DMBA, 1% croton oil in acetone, 3x/wk Grp 5: single topical dose 100 µg DMBA in 100 µl acetone; after 2 wks, 500 mg/kg bw RE extract by gavage for 15 days and 1% croton oil in acetone 3x/wk Grp 6: single topical dose 100 µg DMBA in 100 µl acetone; 500 mg/kg bw RE by gavage 7 days before DMBA until study end; 2 wks after DMBA, 1% croton oil in acetone, 3x/wk	-a stat sig decrease in tumor number, diameter, and weight and a stat sig increase in the avg. latency period was observed in grps given RE compared to Grp 3 (the carcinogen-control grp) - blood serum and liver lipid peroxidation level was stat sig decreased in all RE grps compared to grp 3 - Grp 6 had the greatest changes for all the above parameters - no tumors were found in animals given RE only - RE had no effect on body weight gains	101

Table 12. Anti-tumor activity

Test Article	Extraction Solvent/Method	Dose/Exposure Route	Species No./Group	Tumor Type	Carcinogenicity Model	Results	Reference
Rosmarinus Officinalis (Rosemary) Leaf Extract	DDW	1000 mg/kg bw in DDW; gavage	Swiss albino mice; 12M/grp	skin	DMBA-initiated and croton oil-promoted skin tumorigenesis -same protocol as above (Grps 1-6), except 1000 mg/kg bw RE was used	- stat sig decrease in tumor burden and tumor yield, and a stat sig increase in avg. latency period, in grps given RE compared to Grp 3 (the carcinogen-control grp); tumor incidence was decreased - blood serum lipid peroxidation level was stat sig decreased in all RE grps, and the liver glutathione levels stat sig increased, compared to grp 3 - RE did not cause any adverse effects; no tumors were seen in the RE-only grp.	102
Rosmarinic Acid	-----	100 mg/kg bw in 1 ml distilled water; gavage	Swiss albino mice; 6M/grp	skin	Grp 1: 0.1 ml acetone applied 2x/wk for 8 wks Grp 2: 25 µg DMBA in 100 µl acetone, 2x/wk for 8 wks Grp 3: 25 µg DMBA in 100 µl acetone, 2x/wk for 8 wks; rosmarinic acid was given orally 3x/wk for 25 wks, starting 1 wk before DMBA Grp 4: rosmarinic acid only throughout study	- oral administration of rosmarinic acid with DMBA completely prevented tumor incidence, burden, and volume seen with DMBA only; hyperplasia and mild dysplasia were observed in Grp 3 - stat sig decreases in cytochrome P_{450} and b_5 and increases in GST, GR, and GSH in Grp 3 compared to Grp 2 -rosmarinic acid alone did not affect body or liver wts	103
Rosmarinus Officinalis (Rosemary) Extract	not specified	1.0%, in diet	Sprague-Dawley rats; 20F/grp	mammary	- rats were fed untreated or RE-supplemented diet throughout the study (16 wks post-DMBA) - after 27 days of the test diet, each rat was dosed with 30.9 mg/kg bw DMBA in corn oil by gavage	- the incidence of palpable mammary tumors was less in the RE-fed rats than the controls; at study termination, the tumor incidence was 47% less; this difference was stat sig - the difference in tumors per tumor-bearing rat was not stat sig btwn the two grps - at study termination, 94% and 90% of tumor-bearing rats of the control and RE groups, respectively, possessed mammary adenocarcinomas - RE had no effect on body wt	104
Rosmarinic Acid	-----	100 mg/kg bw in liquid paraffin; gavage	golden Syrian hamsters; 10M/grp	oral	DMBA-induced hamster buccal pouch carc. Grp 1: liquid paraffin, 3x/wk for 14 wks, on left buccal pouch Grp 2: 0.5% DMBA in liquid paraffin, 3x/wk for 14 wks, on left buccal pouch Grp 3: 0.5% DMBA in liquid paraffin, 3x/wk for 14 wks, on left buccal pouch; also, 100 mg/kg bw rosmarinic acid, from 1 wk prior to DMBA until study termination, rosmarinic acid on alternate days Grp 4: rosmarinic acid on alternate days only	- 100% tumor incidence in Grp 2; dosing with rosmarinic acid (Grp 3) completely prevented formation of oral squamous cell carcinoma - severe hyperplasia, moderated keratosis, and mild dysplasia observed in Grp 3 - in Grp 2, stat sig increases in cytochrome P_{450} and b_5 and in GST and GSH; these increases were not seen in Grp 3	105

Table 12. Anti-tumor activity

Test Article	Extraction Solvent/Method	Dose/Exposure Route	Species No./Group	Tumor Type	Carcinogenicity Model	Results	Reference
Rosmarinic Acid	-----	0.3%, in the diet	C57BL/6J Min/+ (*Apc*^{Min}) mice; 6-7M and 6-7F/grp	colorectal	*Apc*^{Min} mouse model of colorectal carc. - 0 or 0.3% rosmarinic acid in feed for 8 wks	- non-stat sig decrease (35%) in total adenoma burden in small intestine and colon; decrease was greater in the colon (54%; non-stat sig) - stat sig increase in small adenomas (<1 mm) in the colon and small intestine - stat sig decrease in the number of large adenomas (>3 mm)	[94]

Abbreviations: B(a)P – benzo[a]pyrene; DDW – double-distilled water; DMBA – 7,12-dimethylbenz[a]anthracene; grp – group; GR – glutathione reductase; GSH – reduced glutathione; GST – glutathione-s-transferase; RE – Rosmarinus officinalis (rosemary) leaf extract; stat sig – statistically significant; TPA – 12-*O*-tetradecanoylphorbol-13-acetate

Table 13. Case reports with *Rosmarinus officinalis* (rosemary)

Mode of Contact	Indication	Patch Testing	Reference
cosmetics and cleansing gel containing 0.1% Rosmarinus officinalis (rosemary) leaf extract	itchy erythema of the face; red papules around the eyes and on the nose and cheeks	patch test with cosmetics and 1% aq. cleansing gel gave positive result (+) to gel only on D3 - patch tested gel ingredients, only positive reaction (+) was to 0.1% aq. Rosmarinus officinalis (rosemary) leaf extract on D3	62
occupational exposure to a Rosmarinus officinalis (rosemary) leaf extract	severe hand, forearm, and face dermatitis	patch tested with 5 and 10% extract in petrolatum; + reaction to 5 and 10% on D2 and D5; 1 control was negative - patch tested with carnosol in ethanol; ?+ reaction to 0.1% at 3 and D7, + reaction to 1% on D3 and D7; controls were negative to 0.1 (n=110) and 1% (n=116) carnosol	63
occupational use of essential aromatherapy oils (5 cases)	hand eczema in all; other involvement seen	- patch testing with the European baseline series, fragrance series, and 2% of each essential oil in petrolatum; ++ reaction to rosemary oil in 2 subjects, + in one, among other positive reactions	64
history of eating foods spiced with rosemary	severe cheilitis	patch tested with 41 antigens, 21 flavoring agents and dyes, and medications; ++ on D2 and + on D5 to rosemary (also + to nickel on D2 and D5; + to wood tars on D2)	65
picked rosemary leaves	developed hand, forearm, and face dermatitis within hours	prick-by-prick testing was negative at 15 min and positive (++) at D2 - patch testing gave positive reactions with rosemary (++) and thyme (+) on D2 and D4 - a photopatch test (10 J/cm) with rosemary and thyme showed stronger reactions (+++ and ++, respectively, on D4) - 5 controls were negative	66
walked near, and touched, odorous plants	cutaneous lesions on the hand and face; developed edema and eczematous lesions on her hands, eyelids, and face	patch and photopatch test with 1% rosemary extract was positive (+++) - patch and photopatch test with rosemary leaves was positive; more intense with photopatch (++/+++) - hydrophilic and lipophilic rosemary extracts 10%, patch and photopatch tests were positive - patch test with 0.1% carnosol in alcohol was positive - patch test with sage and oregano were negative -5 controls were negative with all	67
rosemary leaf plasters applied to knee	after 3 days, acute dermatitis in the application area	positive (++ on D2; +++ on D4) reactions in a patch test with rosemary leaves, but not thyme, origanum, or mint - 10 controls did not react to rosemary leaves	68
applied a poultice containing rosemary and thyme	after 24 h, acute, cutaneous, eczematous lesion on right thigh, with vesicles and blisters	positive patch test results with the poultice (++ on D2 and D4); rosemary (++ on D2 and D4); thyme (- on D2, ++ on D4); and colophony (+ on D2 and D4); negative results with arnica, chamomile, and horsetails - 12 controls were negative with rosemary and thyme	69
rosemary alcohol applied to chest	swelling of face, chest, and dorsal aspect of arms, followed by peeling	positive reactions were found in patch test with fresh Rosmarinus officinalis (rosemary) leaves (+++ on D2, D3, D4), dry rosemary leaves (+ reaction on D2, D3, D3), dry leaves wetted with water (+ reaction on D2, D3, D3), the flower (++ reaction on D2, D3, D3), and rosemary alcohol ((+ reaction on D2, D3, D3) - negative reactions to 50% aq. rosemary alcohol - positive reactions were also found with sage and lavender	70

REFERENCES

1. Gottschalck TE and Breslawec H. International Cosmetic Ingredient Dictionary and Handbook. Washington, DC: Personal Care Products Council, 2012.

2. Petersen M and Simmonds MSJ. Rosmarinic acid. *Phytochemistry*. 2003;62(2):121-125.

3. Bissett NG (ed). Rosmarini folium. In: *Herbal Drugs and Phytopharmaceuticals*. Stuttgart: Medpharm; 1994:428-430.

4. Fleming T (ed). Rosmarinus officinalis. In: *PDR for Herbal Medicines*. 1st ed. Montvale, NJ: Medical Economics Company, Inc; 1998:1101-1103.

5. Cronin H and Draelos ZD. Top 10 botanical ingredients in 2010 anti-aging creams. *J Cosmet Dermatol*. 2010;9(3):218-225.

6. Leung AY and Foster S. Encyclopedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics. 2nd *ed*. New York, NY: John Wiley & Sons, Inc., 1996.

7. Al-Sereiti MR, Abu-Amer KM, and Sen P. Pharmacology of rosemary (*Rosmarinus officinalis* Linn.) and its therapeutic potentialsq. *Indian J Exp Biol*. 1999;37:124-130.

8. Merck, Sharpe, & Dohme Corp. Rosmarinic acid, monograph 10300. http://themerckindex.cambridgesoft.com/themerckindex/Forms/Search/ContentArea/ChemBioVizSearch.aspx?FormGroupId=200000&AppName=THEMERCKINDEX&AllowFullSearch=true&KeepRecordCountSynchronized=false&SearchCriteriaId=23&SearchCriteriaValue=rosmarinic acid&CurrentIndex=0. Date Accessed 5-10-2013.

9. Furtado RA, Rezende de Araújo FR, Resende FA, Cunha WR, and Tavares DC. Protective effect of rosmarinic acid on V79 cells evaluated by the micronucleus and comet assays. *J Appl Toxicol*. 2009;30:254-259.

10. Pereira P, Tysca D, Oliveira P, da Silva Brum LF, Picada JN, and Ardenghi P. Neurobehavioral and genotoxic aspects of rosmarinic acid. *Pharmacological Research*. 2005;52:199-203.

11. Council of Experts, United States Pharmacopeial Convention. Food Chemicals Codex. 8 *ed*. Rockville, MD: United States Pharmacopeia (USP), 6-1-2013.

12. European Food Safety Authority (EFSA). Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission on the use of rosemary extracts as a food additive. *The EFSA Journal*. 2008;721:1-29.

13. Natural Sourcing. Rosemary antioxidant extract - 14% diterpene phenols. [pamphlet]. Oxford, CT: Natural Sourcing LLC; 2013.

14. Natural Sourcing. Rosemary antioxidant extract- 25% diterpene phenols. [pamphlet]. Oxford, CT: Natural Sourcing LLC; 2013.

15. Flavex Naturextrakte GmbH. Rosemary antioxidant extract 25% diterpene phenols, type no. 027.020 [pamphlet]. 2010.

16. Bouhlal K, Meynadier J, Peyron J-L, and Meynadier J. The cutaneous effects of the common concretes and absolutes used in the perfume industry. *J Essent Oil Res*. 1989;1(4):169-195.

17. Council of Experts, United States Pharmacopeial Convention. Food Chemicals Codex. 8th *ed*. Rockville, MD: United States Pharmacopeia (USP), 2012.

18. Maistro EL, Mota SF, Lima EB, Bernardes BM, and Goulart FC. Genotoxicity and mutagenicity of *Rosmarinus officinalis* (Labiatae) essential oil in mammalian cells *in vivo*. *Genetics and Molecular Research*. 2010;9(4):2113-2122.

19. Natural Sourcing. Organic rosemary oil extract. [pamphlet]. Oxford, CT: Natural Sourcing LLC; 2013.

20. Eggensperger H, Wilker M, and Bauer P. Rosmarinic acid. A natural multiactive substance for cosmetics and dermatology. Part 2. Combinations of rosmarinic acid with other natural ingredients. *SOFW Journal*. 1998;124(10):634-636,639.

21. Flavex Naturextrakte GmbH. Certificate of Analysis: Rosemary antioxidant extract, type 027.020 25% diterpene phenols [pamphlet]. 2013.

22. Natural Sourcing. $C0_2$ Rosemary Extract Select Certificate of Analysis. [pamphlet]. Oxford, CT: Natural Sourcing LLC; 2011.

23. Natural Sourcing. Organic Rosemary Antioxidant $C0_2$ Extract 14% Diterpene Phenols Certificate of Analysis. [pamphlet]. Oxford, CT: Natural Sourcing LLC; 2012.

24. Natural Sourcing. Organic Rosemary Antioxidant $C0_2$ Extract 25% Diterpene Phenols Certificate of Analysis. [pamphlet]. Oxford, CT: Natural Sourcing LLC; 2013.

25. Flavex Naturextrakte GmbH. Allergen compounds according to Cosmetic Guideline 76/768/EEC Rosmary antioxidant extact 25% dieterpene phenols, type 027.020 [pamphlet]. 2013.

26. Prevedello M, Veggetti E, and Rapelli S. Essential oils and the antioxidant compounds from *Rosmarinus officinalis* L. Their rational use in cosmetics. *Journal of Applied Cosmetology*. 1998;16(1):17-25.

27. Anadón A, Martínez-Larrañaga MR, Martìnez MA., Ares I, García-Risco MR, Señoráns FJ, and Reglero G. Acute oral safety study of rosemary extracts in rats. *J Food Prot*. 2008;71(4):790-795.

28. Munné-Bosch S and Alegre L. Subcellular compartmentation of the dieterpene carnosic acid and its derivatives in the leaves of rosemary. *Plant Physiology*. 2001;125:1094-1102.

29. Diab Y, Auezova L, Chebib H, Chalchat J-C, and Figueredo G. Chemical composition of Lebanese rosemary *(Rosmarinus officinalis* L.) essential oil as a function of the geographical region and the harvest time. *J.Essent .Oil Res*. 2002;14(6):449-452.

30. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database.* 2013. Dated Jan 15.

31. Personal Care Products Council. 5-31-2013. Updated concentration of Use by FDA Product Category: *Rosmarinus officinalis*-Derived Ingredients (added rosemary leaf oil). Unpublished data submitted by Personal Care Products Council. 4 pages.

32. Personal Care Products Council. 7-29-2013. Concentration of use by FDA Product Category: Rosmarinic Acid. Unpublished data submitted by Personal Care Products Council. 1 pages.

33. Bremmer HJ, Prud'homme de Lodder LCH, and Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. Report No. RIVM 320104001/2006. pp. 1-77.

34. Johnsen MA. The influence of particle size. *Spray Technology and Marketing*. 2004;14(11):24-27.

35. Rothe H. Special Aspects of Cosmetic Spray Evalulation. 9-26-2011. Unpublished data presented at the 26 September CIR Expert Panel meeting. Washington, D.C.

36. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 2011;205(2):97-104.

37. European Commission. Cosmetics Directive (v.1). http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.results. Date Accessed 2-11-2013.

38. European Commission. *Official Journal of the European Union.* Cosmetic Directive 2010/69/EU of 22 October 2010 amending the Annexes of the European Parliament and Council Directive 95/2/EC on food additives other than colours and sweeteners. 2010.

39. Merck, Sharpe, & Dohme Corp. Rosemary; monograph number: 8264. http://themerckindex.cambridgesoft.com/themerckindex/Forms/Search/ContentArea/ChemBioVizSearch.aspx?FormGroupId=200000&AppName=THEMERCKINDEX&AllowFullSearch=true&KeepRecordCountSynchronized=false&SearchCriteriaId=23&SearchCriteriaValue=rosemary&CurrentIndex=0. The Merck Index. Date Accessed 2-12-2013.

40. World Health Organization (WHO). WHO monographs on selected medicinal plants. Geneva, Switzerland: WHO Press, 2009.

41. Ritschel WA, Starzacher A, Sabouni A, Hussain AS, and Koch HP. Percutaneous absorption of rosmarinic acid in the rat. *Meth and Find Exp Clin Pharmacol*. 1989;51(345):352.

42. Nakazawa T and Ohsawa K. Metabolism of rsomarinic acid in rats. *J Nat Prod*. 1998;61:993-996.

43. Baba S, Osakabe N, Natsume M, and Terao J. Orally administered rosmarinic acid is present as the conjugated and/or mehylated forms in plasma, and is degraded and metabolized to conjugated forms of caffeic acid, ferulic acid and *m*-coumaric acid. *Life Sciences*. 2004;75:165-178.

44. Konishi Y, Hitomi Y, Yoshida M, and Yoshioka E. Pharmacokinetic study of caffeic and rosmarinic acid in rats after oral administration. *J Agric Food Chem*. 2005;53:4740-4746.

45. Wang L-H, Wang C-C, and Kuo S-C. Vehicle and enhancer effects on human skin penetration of aminophylline from cream formulations: evaluation *in vivo*. *J Cosmet Sci*. 2007;58(3):245-254.

46. Osakabe N, Takano H, Sanbongi C, Yasuda A, Yanagisawa R, Inoue K, and Yoshikawa T. Anti-inflammatory and anti-allergic effect of rosmarinic acid (RA); inhibition of seasonal allergic rhinoconjunctivitis (SAR) and its mechanism. *BioFactors*. 2004;21:127-131.

47. Mengoni ES, Vichera G, Rigano LA, Rodriguez-Puebla ML, Galliano SR, Cafferata EE, Pivetta OH, Moreno S, and Vojnov A. Suppression of COX-2, IL-1β and TNF-α expression and leukocyte infiltration in inflamed skin by bioactive compounds from *Rosmarinus officinalis* L. *Fitoterapia*. 2011;82(3):414-421.

48. Huang M-T, Ho C-T, Wang ZY, Ferraro T, Lou Y-R, Stauber K, Ma W, Georgiadis C, LAskin JD, and Conney AH. Inhibition of skin tumorigenesis by rosemary and its constituents carnosol and ursolic acid. *Cancer Research*. 1994;54:701-708.

49. Martin R, Pierrard C, Lejeune F, Hilaire P, Breton L, and Bernerd F. Photoprotective effect of a water-soluble extract of *Rosmarinus officinalis* L. against UV-induced matrix metalloproteinase-1 in human dermal fibroblasts and reconstructed skin. *Eur J Dermatol*. 2008;18(2):128-135.

50. Lee J, Kim YS, and Park D. Rosmarinic acid induces melanogenesis through protein kinase A activation signaling. *Biochem Pharmacol*. 2007;74(7):960-968.

51. Nusier MK, Bataineh HN, and Daradkah HM. Adverse effects of rosemary (*Rosmarinus officinalis* L.) on reproductive function in adult male rats. *Exp Biol Med*. 2007;232:809-813.

52. Lemonica IP, Damasceno Dc, and di-Stasi LC. Study of the embryotoxic effects of an extract of rosemary (Rosmarinus officinalis L.). *Braz J Med Biol Res*. 1996;29(2):223-227.

53. PDR for Herbal Medicines. 1st *ed*. Montvale, NJ: Medical Economics Company, Inc, 1998.

54. Herbal Drugs and Phytopharmaceuticals. Stuttgart: Medpharm, 1994.

55. Zhu BT, Loder DP, Cai MX, Ho C-T, Huang M-T, and Conney AH. Dietary administration of an extract from rosemary leaves enhances the liver microsomal metabolism of endogenous estrogens and decreases their uterotropic action in CD-1 mice. *Carcinogenesis*. 1998;19(10):1821-1827.

56. Ohta R, Takagi A, Ohmukai Ho, Marumo H, Ono A, Matsushima Y, Inoue T, Ono H, and Kanno J. Ovariectomized mouse uterotrophic assay of 36 chemicals. *J Toxicol Sci*. 2012;37(5):879-889.

57. Greenlee H, Atkinson C, Stanczyk FZ, and Lampe JW. A pilot and feasibility study on the effects of naturopathic botanical and dietary interventions on sex steriod hormon metabolism in premenopausal women. *Cancer Epidemiol Biomarkers*. 2007;16(8):1601-1609.

58. Komeh-Nkrumah SA, Nanjundaiah SM, Rajaiah R, Yu H, and Moudgil KD. Topical dermal application of essential oils attenuates the severity of adjuvant arthritis in Lewis rats. *Phytother Res*. 2012;26(1):54-59.

59. Opdyke DL. Fragrance raw materials monographs: Rosemary oil. *Food and Cosmetics Toxicology*. 1974;12(7-8):977-978.

60. Mencherini T, Picerno P, Russo OP, Meloni M, and Aquino R. Composition of the fresh leaves and stems of *Melissa officinalis* and evaluation of skin irritation in a reconstituted human epidermis model. *J Nat Prod*. 2009;72:1512-1515.

61. Guin JD. Use of consumer product ingredients for patch testing. *Dermatitis*. 2005;16(2):71-77.

62. Inui S and Katayama I. Allergic contact dermatitis induced by rosemary leaf extract in a cleansing gel. *Journal of Dermatology*. 2005;3253:667179-669180.

63. Hjorther AB, Christophersen C, Hausen BM, and Menné T. Occupational allergic contact dermatitis from carnosol, a naturally-occurring compound present in rosemary. *Contact Dermatitis*. 1997;37(3):99-100.

64. Trattner A, David M, and Lazarov A. Occupational contact dermatitis due to essential oils. *Contact Dermatitis*. 2008;58(5):282-284.

65. Guin JD. Rosemary cheilitis: one to remember. *Contact Dermatitis*. 2001;45(1):63.

66. Armisén M, Rodríguez V, and Vidal C. Photoaggravated allergic contact dermatitis due to *Rosmarinus officinalis* cross-reactive with *Thymus vulgaris*. *Contact Dermatitis*. 2003;48(1):52-53.

67. Serra E, Vila A, Peramiquel L, Dalmau J, Granel C, and Alomar A. Allergic contact dermatitis due to rosemary. *Contact Dermatitis*. 2005;53(3):179-180.

68. Fernandez L, Duque S, Sanchez I, Quiñones D, Rodriquez F, and Garcia-Abujeta JL. Allergic contact dermatitis from rosemary (*Rosmarinus officinalis* L.). *Contact Dermatitis*. 1997;37(5):248-249.

69. Martínez-González MC, Buján JJG, Gómez WM, and Capdevila EF. Concomitant allergic contact dermatitis due to *Rosmarinus officinalis* (rosemary) and *Thymus vulgaris* (thyme). *Contact Dermatitis*. 2007;56(1):49-50.

70. González-Mahave I, Lobesa T, del Pozo MD, Blasco A, and Venturini M. Rosemary contact dermatitis and cross-reactivity with other labiate plants. *Contact Dermatitis*. 2006;54(4):210-212.

71. Natural Sourcing. Rosemary Essential Oil Certificate of Analysis. [pamphlet]. Oxford, CT: Natural Sourcing LLC; 2012.

72. Sigma-Aldrich. Rosmarinic acid. http://www.sigmaaldrich.com/catalog/product/aldrich/536954?lang=en&region=US. Date Accessed 3-7-2013.

73. Advanced Chemistry Development (ACD/Labs) Software. 11.02. 2013.

74. Duke JA. Dr. Duke's Phytochemical and Ethnobotanical Databases. Chemicals in *Rosmarinus officinalis* L. (Lamiaceae) -- rosemary. http://www.ars-grin.gov/duke/. Date Accessed 2-19-2013.

75. Committee of Experts on Cosmetic Products. Plants in Cosmetics. Plants and plant preparations used as ingredients for cosmetic products. Strasbourg: Council of Europe Publishing, 2002.

76. Fahim FA, Esmat AY, Fadel HM, and Hassan KFS. Allied studies on the effect of Rosmarinus officinalis L. on experimental hepatotoxicity and mutagenesis. *Int J Food Sci Nutr*. 1999;50(6):413-427.

77. Aronson DB, Bosch S, Gray DA, Howard PH, and Guiney PD. A comparative human health risk assessment of *p*-dichlorobenzene-based toilet rimblock products versus fragrance/surfactant-based alternatives. *Journal of Toxicology and Environmental Health, Part B: Critical Reviews*. 2007;10(7):467-526.

78. de Melo GAN, Grespan R, Fonseca JP, Farinha TO, Silva EL, Romero AL, Bersani-Amado CA., and Cuman RKN. *Rosmarinus officinalis* L. essential oil inhibits in vivo and in vitro leukocyte migration. *Journal of medicinal food*. 2011;14(9):944-946.

79. Jiang Y, Wu N, Fu Y-J, Wang W, Luo M, Zhao C-J, Zu Y-G, and Liu X-L. Chemical composition and antimicrobial activity of the essential oil of Rosemary. *Environmental toxicology and pharmacology*. 2011;32(1):63-68.

80. Jalali-Heravi M, Moazeni RS, and Sereshti H. Analysis of Iranian rosemary essential oil: application of gas chromatography-mass spectrometry combined with chemometrics. *Journal of chromatography.A*. 2011;1218(18):2569-2576.

81. Stagos D, Spanou C, Margariti M, Stathopoulos C, Mamuris Z, Kazantzoglou G, Magiatis P, and Kouretas D. Cytogenetic effects of grape extracts (Vitis vinifera) and polyphenols on mitomycin C-induced sister chromatid exchanges (SCEs) in human blood lymphocytes. *J Agric Food Chem*. 2007;55(13):5246-5252.

82. Andersen FA, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Leibler DC, Marks JG, Shank RC, Slaga TJ, and Snyder PW. Final report of the Cosmetic Ingredient Review Expert Panel. Amended safety assessment of Calendula officinalis-derived cosmetic ingredients. *Int J Toxicol*. 2010;29(4):221S-243S.

83. World Health Organization (WHO). International Agency for Research (IARC). Volume 56. Some Naturally Occurring Substances: Food Items and Constituents, Heterocyclic Aromatic Amines and Mycotoxins. Su mmary of data reported and evaluation. http://monographs.iarc.fr/ENG/Monographs/vol56/volume56.pdf. Date Accessed 2-26-2013.

84. Integrated Laboratory Systems. Chlorogenic Acid [327-97-9] and Caffeic Acid [331-39-5]. Review of toxicological literature. http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/ChlorogenicAcid.pdf. Date Accessed 2-26-2013.

85. Doolaege EH, Raes K, de Vos F, Verhe R, and de Smet S. Absorption, distribution and elimination of carnosic acid, a natural antioxidant from Rosmarinus officinalis, in rats. *Plant Food Hum Nutr*. 2011;66(2):196-202.

86. World Health Organization (WHO). International Agency for Research (IARC). Volume 73. Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents and Some Other Substances. Summary of data reported and evaluation. http://monographs.iarc.fr/ENG/Monographs/vol73/volume73.pdf. Date Accessed 7-8-2013.

87. National Toxicology Program (NTP). Testing status of agents at NTP: α-pinene. http://ntp.niehs.nih.gov/?objectid=BD4A21C3-123F-7908-7B76D9A5ADDD10A3. Date Accessed 3-13-2013.

88. National Toxicology Program (NTP). Testing status of agents at NTP: 1,8-cineole. http://ntp.niehs.nih.gov/?objectid=BC9623D7-123F-7908-7BE9A208CC6CB46A. Date Accessed 3-13-2013.

89. Integrated Laboratory Systems. β-Myrcene [123-35-3]. Review of toxicological literature. http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/beta-myrcene_508BE.pdf. Date Accessed 3-13-2013.

90. National Toxicology Program (NTP). NTP Technical Report on the toxicology and carcinogenesis studies of α,β-thujone (CAS No. 76231-76-0) in F34.N rats and B6C3F1 mice. (Gavage studies). 2011. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR570.pdf. Report No. NTP TR 570.

91. World Health Organization (WHO). IARC Monographs on the evaluation of carcinogenic risks to humans. Methyleugenol. http://monographs.iarc.fr/ENG/Monographs/vol101/mono101-013.pdf. Date Accessed 6-3-2013.

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

93. Parnham MJ and Kesselring K. Rosmarinic acid. *Drugs of the Future*. 1985;10:756-757.

94. Karmokar A, Marczylo TH, Cai H, Steward WP, Gescher AJ, and Brown K. Dietary intake of rosmarinic acid by *Apc*^{Min} mice, a model of colorectal carcinogenesis: levels of parent agent in the target tissue and effect on adenoma development. *Mol Nutr Food Res*. 2012;56:775-783.

95. Žegura B, Dobnik D, Niderl MHZ, and Filipic M. Antioxidant and antigenotoxic effects of rosemary *(Rosmarinus officinalis* L.) extracts in *Salmonella typhimurium* TA98 and HepG2 cells. *Environmental toxicology and pharmacology*. 2011;32(2):296-305.

96. Bersani C, Cantoni C, and Soncini G. Ames test valuation of mutagenic activity in essences and spices. *Arch Vet Ital*. 1981;32:10-11.

97. Gaiani TF, Carvalho JCT, Silva JMSF, and Maistro EL. Absence of clastogenic effects of the extract from medicinal plant *Rosmarinus officinalis* L. on Wistar rat bone marrow cells. *Cytologia*. 2006;71:101-106.

98. Furtado MA, Fernandes de Almedia LC, Furtado RA, Cunha WR, and Tavares DC. Antimutagenicity of rosmarinic acid in Swiss mice evaluated by the micronucleus assay. *Mutat Res*. 2008;657:150-154.

99. Aleisa AM. Cytological and biochemical effects of St. John's Wort supplement (a complex mixture of St. John's Wort, Rosemary and Spirulina) on somatic and germ cells of Swiss Albino mice. *Int J Environ Res Public Health*. 2008;5(5):408-417.

100. Minnunni M, Wolleb U, Mueller O, Pfiefer A, and Aeschbacher HU. Natural antioxidants as inhibitors of oxygen species induced mutagenicity. *Mutat Res*. 1992;269:193-200.

101. Sancheti G and Goyal PK. Effect of *Rosmarinus officinalis* in modulating 7,12-dimethylbenz(a)anthracene induced skin tumorigenesis in mice. *Phytother Res*. 2006;20(11):981-986.

102. Sancheti G and Goyal PK. Modulatory influence of *Rosmarinus officinalis* on DMBA-induced mouse skin tumorigenesis. *Asian Pacific Journal of Cancer Prevention*. 2006;7:331-335.

103. Sharmila R and Manoharan S. Anti-tumor activity of rosmarinic acid in 7,12-dimethylbenz(a)anthracene (DMBA) induced skin carcinogenesis in Swiss albino mice. *Indian J Exp Biol*. 2012;50:187-194.

104. Singletary KW and Nelshoppen JM. Inhibition of 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumorigenesis and of in vivo formation of mammary DMBA-DNA adducts by rosemary extract. *Cancer Lett*. 1991;60(2):169-175.

105. Anusuya C and Manoharan S. Antitumor initiating potential of rosmarinic acid in 7,12-dmethylbenz(a)anthracene-induced hamster buccal pouch carcinogenesis. *Journal of Environmental Pathology, Toxicology, and Oncology*. 2011;30(3):199-211.

ROSEMARY	02A - Bath Oils, Tablets, and Salts	1
ROSEMARY	04C - Powders (dusting and talcum, excluding aftershave talc	1
ROSEMARY	04E - Other Fragrance Preparation	1
ROSEMARY	05A - Hair Conditioner	2
ROSEMARY	05F - Shampoos (non-coloring)	2
ROSEMARY	10A - Bath Soaps and Detergents	1
ROSEMARY	12A - Cleansing	2
ROSEMARY	12C - Face and Neck (exc shave)	2

ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	02A - Bath Oils, Tablets, and Salts	1
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	02B - Bubble Baths	2
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	03D - Eye Lotion	11
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	03F - Mascara	2
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	03G - Other Eye Makeup Preparations	5
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	05A - Hair Conditioner	35
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	05C - Hair Straighteners	2
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	05E - Rinses (non-coloring)	2
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	05F - Shampoos (non-coloring)	46
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	05G - Tonics, Dressings, and Other Hair Grooming Aids	17
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	05H - Wave Sets	1
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	05I - Other Hair Preparations	9
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	06D - Hair Shampoos (coloring)	1
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	07A - Blushers (all types)	1
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	07C - Foundations	1
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	07E - Lipstick	7
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	07F - Makeup Bases	3
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	07I - Other Makeup Preparations	4
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	10A - Bath Soaps and Detergents	16
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	10E - Other Personal Cleanliness Products	1
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12A - Cleansing	30
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12C - Face and Neck (exc shave)	42
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12D - Body and Hand (exc shave)	17
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12F - Moisturizing	58
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12G - Night	12
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12H - Paste Masks (mud packs)	16
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12I - Skin Fresheners	12
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12J - Other Skin Care Preps	27
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	13A - Suntan Gels, Creams, and Liquids	2
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	13B - Indoor Tanning Preparations	4

ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	03B - Eyeliner	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	03G - Other Eye Makeup Preparations	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	05A - Hair Conditioner	6
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	05B - Hair Spray (aerosol fixatives)	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	05C - Hair Straighteners	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	05F - Shampoos (non-coloring)	8
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	05G - Tonics, Dressings, and Other Hair Grooming Aids	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	05H - Wave Sets	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	05I - Other Hair Preparations	7
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	11A - Aftershave Lotion	4
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	12C - Face and Neck (exc shave)	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	12F - Moisturizing	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	12G - Night	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	12H - Paste Masks (mud packs)	2

ROSMARINUS OFFICINALIS (ROSEMARY) LEAF	02A - Bath Oils, Tablets, and Salts	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF	05A - Hair Conditioner	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF	05F - Shampoos (non-coloring)	10
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF	10E - Other Personal Cleanliness Products	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF	12A - Cleansing	1

ROSMARINUS OFFICINALIS (ROSEMARY) LEAF	12F - Moisturizing	1

ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	01A - Baby Shampoos	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	01B - Baby Lotions, Oils, Powders, and Creams	6
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	02A - Bath Oils, Tablets, and Salts	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	02B - Bubble Baths	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	03B - Eyeliner	12
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	03C - Eye Shadow	6
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	03D - Eye Lotion	11
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	03G - Other Eye Makeup Preparations	7
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	04E - Other Fragrance Preparation	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05A - Hair Conditioner	72
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05B - Hair Spray (aerosol fixatives)	4
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05C - Hair Straighteners	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05D - Permanent Waves	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05E - Rinses (non-coloring)	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05F - Shampoos (non-coloring)	64
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05G - Tonics, Dressings, and Other Hair Grooming Aids	56
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05H - Wave Sets	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05I - Other Hair Preparations	19
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	06B - Hair Tints	22
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	07B - Face Powders	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	07C - Foundations	5
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	07D - Leg and Body Paints	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	07E - Lipstick	24
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	07F - Makeup Bases	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	07I - Other Makeup Preparations	6
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	08A - Basecoats and Undercoats	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	09B - Mouthwashes and Breath Fresheners	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	10A - Bath Soaps and Detergents	38
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	10E - Other Personal Cleanliness Products	7
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	11A - Aftershave Lotion	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	11E - Shaving Cream	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12A - Cleansing	36
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12B - Depilatories	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12C - Face and Neck (exc shave)	73
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12D - Body and Hand (exc shave)	29
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12F - Moisturizing	108
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12G - Night	16
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12H - Paste Masks (mud packs)	11
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12I - Skin Fresheners	8
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12J - Other Skin Care Preps	18
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	13A - Suntan Gels, Creams, and Liquids	5

ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	01A - Baby Shampoos	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	01B - Baby Lotions, Oils, Powders, and Creams	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	01C - Other Baby Products	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	02A - Bath Oils, Tablets, and Salts	18
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	02B - Bubble Baths	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	02D - Other Bath Preparations	5
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	03D - Eye Lotion	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	03G - Other Eye Makeup Preparations	5
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	04A - Cologne and Toilet waters	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	04B - Perfumes	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	04C - Powders (dusting and talcum, excluding aftershave talc	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	04E - Other Fragrance Preparation	19
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	05A - Hair Conditioner	18
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	05B - Hair Spray (aerosol fixatives)	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	05E - Rinses (non-coloring)	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	05F - Shampoos (non-coloring)	42
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	05G - Tonics, Dressings, and Other Hair Grooming Aids	13

ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	05I - Other Hair Preparations	10
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	06D - Hair Shampoos (coloring)	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	07B - Face Powders	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	07D - Leg and Body Paints	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	07I - Other Makeup Preparations	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	09B - Mouthwashes and Breath Fresheners	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	09C - Other Oral Hygiene Products	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	10A - Bath Soaps and Detergents	32
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	10B - Deodorants (underarm)	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	10E - Other Personal Cleanliness Products	6
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	11A - Aftershave Lotion	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	11D - Preshave Lotions (all types)	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	11E - Shaving Cream	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	11G - Other Shaving Preparation Products	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12A - Cleansing	26
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12C - Face and Neck (exc shave)	66
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12D - Body and Hand (exc shave)	61
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12E - Foot Powders and Sprays	4
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12F - Moisturizing	56
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12G - Night	4
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12H - Paste Masks (mud packs)	14
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12I - Skin Fresheners	15
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12J - Other Skin Care Preps	66
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	13A - Suntan Gels, Creams, and Liquids	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	13B - Indoor Tanning Preparations	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF POWDER	12C - Face and Neck (exc shave)	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	05A - Hair Conditioner	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	05F - Shampoos (non-coloring)	10
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	05G - Tonics, Dressings, and Other Hair Grooming Aids	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	07C - Foundations	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	07H - Makeup Fixatives	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	12F - Moisturizing	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	12H - Paste Masks (mud packs)	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	12I - Skin Fresheners	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	12J - Other Skin Care Preps	1
ROSMARINUS OFFICINALIS (ROSEMARY) WATER	12C - Face and Neck (exc shave)	1
Rosmarinic Acid		0

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: April 22, 2013

SUBJECT: Rosmarinus Officinalis (Rosemary) Leaf Extract: Composition Information

Natural Sourcing. 2013. Organic rosemary oil extract.

Natural Sourcing. 2013. Rosemary antioxidant extract - 14% diterpene phenols.

Natural Sourcing. 2013. Rosemary antioxidant extract - 25% diterpene phenols.

Natural Sourcing. 2011. CO_2 Rosemary Extract Select Certificate of Analysis.

Natural Sourcing. 2012. Organic Rosemary Antioxidant CO_2 Extract 14% Diterpene Phenols Certificate of Analysis.

Natural Sourcing. 2013. Organic Rosemary Antioxidant CO_2 Extract 25% Diterpene Phenols Certificate of Analysis.

Natural Sourcing. 2012. Rosemary Essential Oil Certificate of Analysis.

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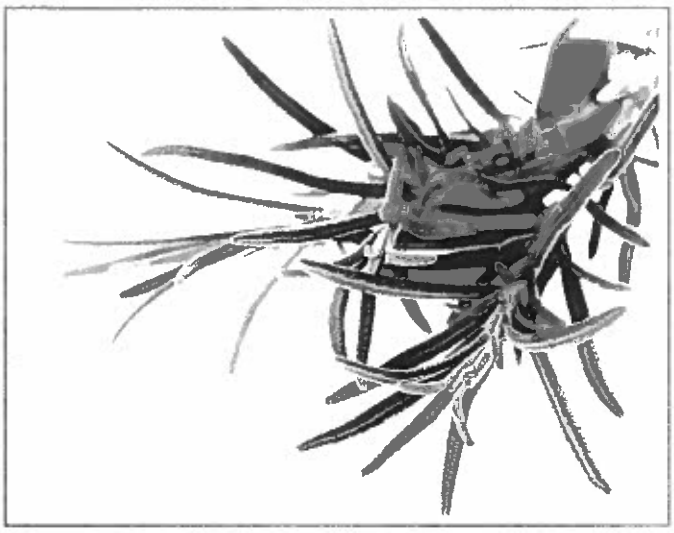

ORGANIC ROSEMARY OIL EXTRACT

Available With 14% Diterpene Phenol or 25% Diterpene Phenol Concentration

INCI: Rosmarinus officinalis (Rosemary) Leaf Oil, Helianthus annuus (Sunflower) Seed Oil and Tocopherols
Extraction Method: CO2 (Supercritical Fluid Extraction)
Shelf Life: > 5 Years With Proper Storage
Country of Origin: Germany

Background:

Botanical Origins provides the most superior Organic Rosemary Oil Extract (ROE) available. Rosemary is a fragrant herb native to the Mediterranean with leaves that resemble needles. Rosemary Oil Extract acts as a natural anti-oxidant suitable for use in nutraceutical and cooking applications. Our Rosemary Oil Extract is carefully extracted from high-grade organic rosemary leaves. Rosemary leaves that possess a high concentration of diterpene phenols are selected. The leaves are then extracted using supercritical fluid extraction via CO2 and a trace amount of alcohol. This extraction method results in a superior quality, natural oil that maintains the most beneficial properties of rosemary including a high DTP concentration. This method is also ideal for maintaining the natural integrity of our oil because other extraction methods commonly use synthetic chemicals that can remain within the final product. A small amount of organic sunflower oil (<4%) is added to increase solubility when blended with oils/fats. A trace amount of natural GMO-free tocopherols are added to enhance the natural anti-oxidant properties of the oil. Our rosemary oil extract is then packaged to maintain its purity, freshness and beneficial compounds.

Applications:

CO2 extracted organic rosemary oil is especially suited to protect against oxidation in food products that contain fats and oils. Suggested uses are within meat products, sauces, marinades, sauces, condiments, and salad dressings.

Rosemary Seed Extract Properties

- Natural Anti-oxidant
- Oil soluble
- Low flavor permits them to be successfully used in all food applications
- Unregulated and can be used in both diet and health foods/ supplements at any desired dosage.
- Please see our Rosemary Oil Extract Specification Sheets for further details.

14% vs. 25% Diterpene Phenol (DTP) Content

Botanical Origins offers both standardized 14% and 25% Diterpene Phenol (DTP) varieties of Organic Rosemary Oil Extract. The higher the DTP content contained with Rosemary Oil Extract, the stronger the anti-oxidation property that the oil possesses.

Dosage Recommendations

A minimum 200ppm of Rosemary Oil Extract 14% DTP is recommended for products containing a low percentage of oils/ fats. Raise the ratio to increase protection against oxidation. If your formulation includes a high concentration of unsaturated fatty acids, a minimum of 2000ppm Rosemary Oil Extract 25% DTP is suggested.

Liquefy the oil extract by heating to 40-50°C (104-122°F) and then add to the oil/fat phase.

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2013

NATURAL SOURCING
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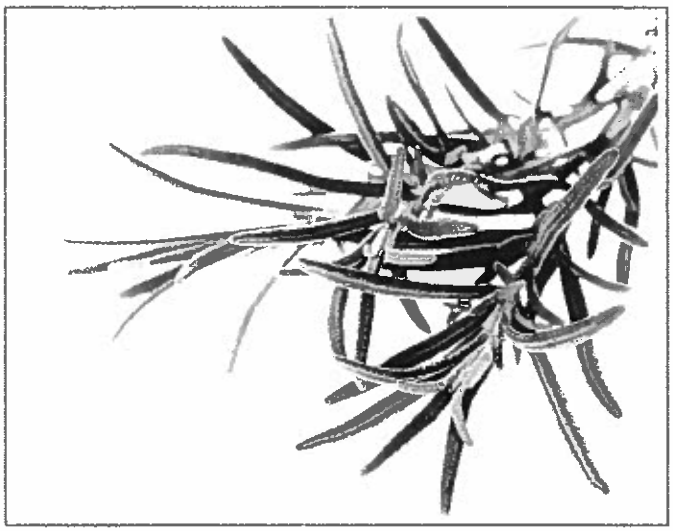

ROSEMARY ANTIOXIDANT EXTRACT

14 % Diterpene Phenols, (organic acc. to USDA NOP)

Contains mainly antioxidative components [2][3]

Raw material:
Rosmorinus officinalis – Leaves (organic acc. To USDA NOP)

Production:
By supercriticol fluid extraction with naturol carbon dioxide and a small omount of ethanol os entroiner. No inorganic salts, no heavy metals, no reproducible microorgonisms (1). The CO2-extract is standardised with sunflower oil (organic acc. To USDA NOP).

Extract:
Dark brown. At room temperature, it is a viscous liquid product with characteristic smell and toste. The product con solidify under cool storage or after standing at room temperature. By warming it up to a temperoture of 105 degrees F, it returns to its viscous, oily consistency.

D/E-Ratio:
5,0 – 7,1 kg row materiol. Yield 1 kg product.

Declaration:
INCI-Name: Rosmarinus Officinalis 1.caf Extract [CO2], CAS-No. 84604-14-8, EINECS-No. 283-291-9 ond Helianthus Annuus Seed Oil, , CAS-No. 8001-21-6. EINECS-No. 232-273-9

Ingredients:
13 - 15 % ontioxidative phenolic diterpenes with > 9 % of cornosolic ocid; essentiol oil < 2 %, water < 5 %, alcohol < 4 %, vegetoble oil, cuticular waxes, GMO-free tocopherols.

Application:
Stabilization of fotty oils, carotenoids, essentiol oils for retarding oxidation; in the food industry (dressings, sausoges, snacks,etc.). Clean label declaration as spice extract without registration number, in cosmetic ointments.
Dosage: 0,02 - 0,1 % in case of saturated fats, 0,2 - 0,4 % in case of polyunsaturated oils.

Naturalness:
This product is 100 % naturol ond contains no other additives other than vegetable oil. It conforms to the Codex Alimentorius definition for naturol extracts.

Stability:
Closed pack under cool storage and exclusion of light at least 5 years.

[1] Manninen P., Höivälä E., Sonmo S., Kallio H.: Z. Lebens Unters Forsch A (1997) 204: 202-205
[2] Quirin K. W., Gerard D.: Cosm. Toil. Manf. Worldw.: 1998, S. 31
[3] Gerard D., Quirin K. W., and Schwarz E.: Food Marketing and Technology October 1995, S. 46-55

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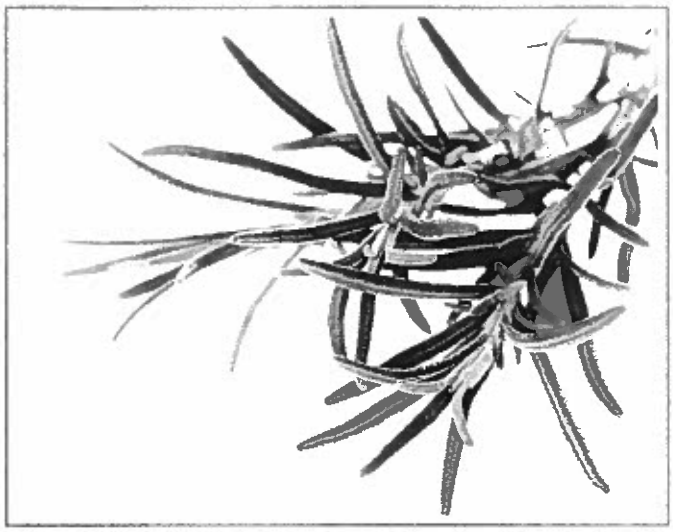

ROSEMARY ANTIOXIDANT EXTRACT

25 % Diterpene Phenols, (organic acc. to USDA NOP)

Cantains mainly antioxidative components [2][3[

Raw material:
Rosmarinus officinalis – Leaves (organic acc. To USDA NOP)

Production:
By supercritical fluid extraction with natural carbon dioxide and a small amount of ethanol as entrainer. No inorganic salts, no heavy metals, no reproducible microorganisms [1]. The CO2-extract is standardised with sunflower oil (organic acc. To USDA NOP).

Extract:
Dark brown. At room temperature, it is a viscous liquid product with characteristic smell and taste. The product can solidify under cool storage or after standing at room temperature. By warming it up to a temperature of 105 degrees F, it returns to its viscous, oily consistency.

D/E-Ratio:
7,1 – 12,0 kg raw material. Yield 1 kg product.

Declaration:
INCI-Name: Rosmarinus Officinalis Leaf Extract [CO2], CAS-No. 84604-14-8, EINECS-No. 283-291-9 and Helianthus Annuus Seed Oil, , CAS-No. 8001-21-6. EINECS-No. 232-273-9

Ingredients:
24 - 26 % antioxidative phenolic diterpenes with at least 14 % of carnosolic acid; content of essential oil < 4 %, water < 5 %, alcohol < 4 %, sunflower oil, cuticular waxes, GMO-free tocopherols.

Application:
Stabilization of fatty oils, carotenoids, essential oils for retarding oxidation; in the food industry (dressings, sausages, snacks,etc.). Clean label declaration as spice extract without registration number, in cosmetic ointments.
Dosage: 0,02 - 0,1 % in case of saturated fats, 0,1 - 0,2 % in case of polyunsaturated oils.

Naturalness:
This product is 100 % natural and contains no other additives other than vegetable oil. It conforms to the Codex Alimentarius definition for natural extracts.

Stability:
Closed pack under cool storage and exclusion of light at least 5 years.

[1] Manninen P., Häivälä E., Sarimo S., Kallio H.: Z. Lebens Unters Forsch A (1997) 204: 202-205

[2] Quirin K. W., Gerard D.: Cosm. Toil. Mauf. Worldw.: 1998, S. 31

[3] Gerard D., Quirin K. W., and Schwarz E.: Food Marketing and Technology October 1995, S. 46-55

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CO2 Rosemary Extract Select

INCI: Rosmarinus officinalis Extract
Lot No: 180405

Certificate of Analysis

Analytical Details	Specifications	Results
Essential Oil Content:	78-88	79%
Volatile Components:	%	%
α-Pinene:	8-12	11.4
Camphene:	n.s.	4.0
β-Pinene:	n.s.	3.7
Myrcene:	n.s.	2.7
p-Cymene:	n.s.	1.2
Limonene:	2-4	2.4
1, 8 Cineole:	>40	41.3
Linalool:	n.s.	0.83
Camphor:	6-13	13.0
Borneol:	n.s.	3.8
α-terpineol:	n.s.	3.9
Verbenone:	n.s.	0.45
Bornyl Acetate:	n.s.	0.94
Caryophyllene:	3-10	4.7
Refractive Index (20°C):	1.4710-1.4740	1.4730
Density (20°C):	0.9165-0.9220	0.9177 g/cm3
Manufacture Date:	October 2008	
Expiration Date:	October 2013	

Date: 07/01/2011

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Organic Rosemary Antioxidant CO2 Extract 14% Diterpene Phenols

INCI: Rosmarinus Officinalis Leaf Extract (CO2) (and) Helianthus Annuus Seed Oil

Lot No: 811410

Certificate of Analysis

Feature	Method	Limits	Value Unit
Analysis of phenolic diterpenes:	HPLC, 21.028.05		
Rosmanol:		Not Specified	0.07%
7-Methyl-Rosmanol:		Not Specified	0.09%
Carnosol:		Not Specified	1.2%
Carnosolic Acid:		Not Specified	10.5%
12-Methyl-Carnosolic Acid:		Not Specified	2.4%
Sum of phenolic diterpenes (calc. about DAS):		13-15%	14.3%
Reference AO Compounds Carnesol + Carnosic Acid (calc as carnosic acid):		Not Specified	9.5%
Ursolic Acid:		Not Specified	0.43%
Oleanolic Acid:		Not Specified	0.62%
Content of Essential Oil:	21.006.01, GCMS	< 2%	1.9%
Residual content of ethanol:	GCFID, 21.025.01	< 2%	0.71%
Content of water:	Karl Fischer Titr.	< 1%	0.30%
Manufacture Date:	December 2011		
Expiration Date:	December 2016		

Antioxidative activity compared with 500 ppm tocopherol
(Rancimat test in lard at 120°C and 15 Liter/hour air flow)

Dosage Rosemary Antioxidant	Relation to 500 ppm tocopherol
200 ppm	Equivalent activity
500 ppm	1.3 times stronger activity

Date: 03/22/2012

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Organic Rosemary Antioxidant CO2 Extract

25% Diterpene Phenols

INCI: Rosmarinus Officinalis Leaf Extract (CO2) (and) Helianthus Annuus Seed Oil

Lot No: 311418

Certificate of Analysis

Feature	Method	Limits	Value Unit
Rosmanol:	21.028.05 HPLC	Not Specified	0.13%
7-Methyl-Rosmanol:	21.028.05 HPLC	Not Specified	0.18%
Carnosol:	21.028.05 HPLC	Not Specified	1.4%
Carnosolic Acid:	21.028.05 HPLC	> 14%	18.7%
12-Methyl-Carnosolic Acid:	21.028.05 HPLC	Not Specified	4.5%
Sum of phenolic diterpenes (calc. about DAS):	21.028.05 HPLC	24-26%	24.9%
Ursolic Acid:	21.028.05 HPLC	Not Specified	0.29%
Oleanolic Acid:	21.028.05 HPLC	Not Specified	0.51%
Content of Essential Oil:	21.006.01, Distillation	< 4%	3.0%
Residual content of ethanol:	GCFID, 21.025.01	< 2%	0.39%
Content of water:	Karl Fischer Titr.	< 1%	0.91%
Date of Manufacture:	October 2011		
Best Before:	October 2016		

Antioxidant activity compared with 500 ppm tocopherol (Rancijat test in lard at 120°C and 15 liter/hour air flow)

Dosage Rosemary Antioxidant	Relation to 500 ppm tocopherol
200 ppm	**1.2 times stronger activity**
500 ppm	**1.6 times stronger activity**

Date: 03/14/2013

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Rosemary Essential Oil

INCI: Rosmarinus officinalis (Rosemary) Oil
Lot No: ROSOFF011612
CAS No: 8000-25-7 FEMA No: 2992

Certificate of Analysis

Analytical Details	Specifications	Results
Odor:	Camphorous	Conforms
Color:	Pale yellow to pale green to colorless	Conforms
Density @ 20°C:	0.907-0.920	Conforms
Refractive Index:	1.464-1.472	Conforms
Optical Rotation:	-2 ° to + 5 °	Conforms
Flash Point:		43°C
Analysis by GC, FID:		
Approximate α-pinene:		8-14%
Approximate Cineol-1,8:		Complies with standard
Chemical Class:		Oxide
Manufacture Date:	01/16/2012	
Expiration Date:	01/16/2014	

Date: 03/28/2012

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Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: May 31, 2013

SUBJECT: Rosmarinus Officinalis (Rosemary) Leaf Extract

Flavex Naturextrakte GmbH. 2010. Rosemary antioxidant extract 25% diterpene phenols, type no. 027.020.

Flavex Naturextrakte GmbH. 2013. Certificate of Analysis: Rosemary antioxidant extract, type no. 027.020 25% diterpene phenols.

Flavex Naturextrakte GmbH. 2013. Allergen compounds according to Cosmetic Guideline 76/768/EEC Rosemary antioxidant extract 25% diterpene phenols, type no. 027.020.

Official Journal of the European Union. 2010. Commission Directive 2010/69/EU of 22 October 2010 amending the Annexes to European Parliament and Council Directive 95/2/EC on food additives other than colours and sweeteners.
See p.24 and 29 of this document
See also the EFSA 2008 opinion on the use of rosemary extracts as a food additive (previously provided)

Weckesser S, Engel K, Simon-Haarhaus B, et al. 2007. Screening of plant extracts for antimicrobial activity against bacteria and yeasts with dermatological relevance. Phytomedicine 14: 508-516.
provided in a separate file

Reuter J, Jocher A, Hornstein S, et al. 2007. Sage extract rich in phenolic diterpenes inhibits ultraviolet-induced erythema in vivo. Planta Med 73:1-2.
Please note that sage contains exactly the same phenolics as rosemary, and that the essential oils, which differ between the two species, are removed from both extracts.
provided in a separate file

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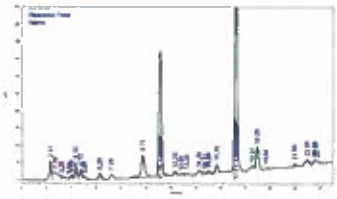
Rosemary Antioxidant extract
25 % Diterpene Phenols, Type no. 027.020

contains mainly antioxidative components [2][3]



Raw material:
Rosmarinus officinalis - Leaves, dried

Production:
By supercritical fluid extraction with natural carbon dioxide and a small amount of ethanol as entrainer, no inorganic salts, no heavy metals, no reproducible microorganisms [1]. The essential oil is widely removed by multistep separation.The antioxidative CO2-extract is standardised with sunflower oil (organic).

Extract:
Dark brown and at room temperature viscous liquid product with weak flavour. The product can lose his ability to flow at cool storage or standing for a longer period at room temperature. However by warming up to 40° C it gets back his oily consistency.

D/E - ratio:
7,1 - 12,0 kg raw material yield 1 kg product.

Declaration:
INCI-Name (CTFA): Rosmarinus Officinalis (Rosemary) Leaf Extract, CAS-No. 84604-14-8, EINECS-No. 283-291-9 and Helianthus Annuus (Sunflower) Seed Oil, CAS-No. 8001-21-6, EINECS-No. 232-273-9

Transport data:
No dangerous good in the sense of the transport regulations.

Ingredients:
24 - 26 % total antioxidative phenolic diterpenes with > 16 % of carnosic acid; essential oil 1 - 4% , water < 1 %, alcohol < 2 %, sunflower oil (organic), cuticular waxes.

Application:
The product has antioxidative, antimicrobial and antiinflammatory property; for retarding oxidation of fatty oils, carotenoids, essential oils; in the food industry (dressings, sausages, snacks,etc.), in food supplements and in cosmetics;
dosage: 0,02 - 0,05 % in case of saturated fats, 0,1 - 0,2 % in case of polyunsaturated oils
In EU declaration as Antioxidant: Rosemary Extract or Antioxidant: E 392 if used in food and supplements.

Naturalness:
The product is manufactured from the named raw material. It contains apart from the sunflower oil (organic) no additives and no other technical adjuncts. The product is 100 % natural and corresponds to the EC Flavouring Regulation No. 1334/2008 for flavouring preparations.

Stability:
Unopened container under cool and dry storage conditions and exclusion of light at least 5 years.

[1] Manninen P., Häivälä E., Sarimo S., Kallio H. : Z. Lebens Unters Forsch A (1997) 204: 202-205
[2] Quirin K. W., Gerard D.: Cosm. Toil. Mauf. Worldw.: 1998, S. 31
[3] Gerard D., Quirin K. W., and Schwarz E.: Food Marketing and Technology October 1995, S. 46-55

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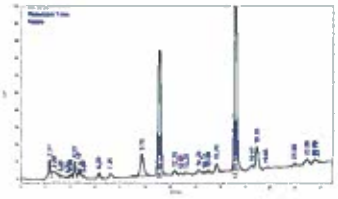
CO_2-Extraction Authentic Quality secured by FLAVEX

CO_2 EXTRACTION

Rosemary Antioxidant extract
25 % Diterpene Phenols, Type no. 027.020

These data are given for customer's information only to the best of our knowledge but under exemption of liability especially regarding infringement of or prejudice to third party rights through the use of this product. This information is not a substitute for prior tests demonstrating the suitability of the product for the intended use. Users are responsible for ensuring the compliance with the applicable legislation. The concentrated FLAVEX extracts are raw materials for product formulation. Hence they are not intended for direct consumption in food and for undiluted topical application in cosmetics, perfumery and aromatherapy. Keep away from children.



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CO_2 EXTRACTION

Hochdruckextraktion mit CO_2

FLAVEX®
Naturextrakte GmbH

Certificate of Analysis

Rosemary Antioxidant extract, type no. 027.020

25 % Diterpene Phenols

batch no. 431022, lab no. 14132

production: January 2013 retest: January 2018

raw material: *Rosmarinus officinalis* - Leaves, dried

country of origin of drug: Spain

country of origin of product: Germany

D/E - ratio: 7,1 - 12,0 kg raw material yield 1 kg product.

analytical results:

feature	method	limits	value	unit
Rosmanol	21.028.05, HPLC	n.s.	0,t3	%
7-Methyl-Rosmanol	21.028.05, HPLC	n.s.	0,32	%
Carnosol	21.028.05, HPLC	n.s.	2,9	%
Carnosic Acid	21.028.05, HPLC	> t6	20,6	%
12-Methyl-Carnosic Acid	21.028.05, HPLC	n.s.	1,0	%
Sum of phenolic diterpenes (calculated about DAS)	21.028.05, HPLC	24 - 26	25,0	%
Reference AO Compounds Carnosol + Carnosic Acid (calc. as Carnosic Acid)	21.028.05, HPLC	12 - 16	15,7	%
Ursolic Acid	21.028.05, HPLC	n.s.	0,42	%
Oleanolic Acid	21.028.05, HPLC	n.s.	0,52	%
Content of essential oil	21.006.01, Distillation	< 4	1,7	% (w/w)
Content of water	Karl Fischer method	< 1	0,15	%
Residual content of ethanol	21.025.01, GCFID	< 2	0,33	%

n.s. = not specified n.d. = not detected

Antioxidative activity compared with 500 ppm tocopherol
(Rancimat test in lard at 120°C and 15 Liter/ hour air flow)

Dosage Rosemary Antioxidant	Relation to 500 ppm tocopherol
200 ppm	1,2 times stronger activity
500 ppm	1,6 times stronger activity

Digitally signed by Anja Cawelius
Reason: Quality control
Date: 2013.02.14 14:39:54 +01'00'

The product meets specification no. 16.188.06; date of analysis: 2013.02.14
This computerized CoA has digital signature validated by FLAVEX QC.

The data in this report of analysis have been determined carefully and to the best of our knowledge. Depending on transport and storage conditions the indicated data can be subject to certain changes which are outside of our influence. Hence the report has not the meaning of a guaranty in the legal sense and does not dispense the customer from making his own quality control before using the product.

CO_2-Extraction · Authentic Quality · secured by FLAVEX

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http://www.flavex.com

ISO 9001:2008 ISO 14001:2004 Umweltpakt Saar

Allergen Compounds according Cosmetic Guideline 76/768/EEC
Rosemary Antioxidant extract
25 % Diterpene Phenols, Type no.: 027.020

Chemical name	CAS no.	Concentration naturally found in extract	
Amyl cinnamal	122-40-7	-	%
Benzyl alcohol	100-51-6	-	%
Cinnamyl alcohol	104-54-1	-	%
Citral	5392-40-5	-	%
Eugenol	97-53-0	-	%
Hydroxy-citronellal	107-75-5	-	%
Isoeugenol	97-54-1	-	%
Amyl cinnamyl alcohol	101-85-9	-	%
Benzyl salicylate	118-58-1	-	%
Cinnamal	104-55-2	-	%
Coumarin	91-64-5	-	%
Geraniol	106-24-1	-	%
Hydroxy-methylpentylcyclohexenecarboxaldehyde	31906-04-4	-	%
Anisyl alcohol	105-13-5	-	%
Benzyl cinnamate	103-41-3	-	%
Farnesol	4602-84-0	-	%
2-(4-tert-Butylbenzyl)propionaldehyde	80-54-6	-	%
Linalool	78-70-6	< 0,1	%
Benzyl benzoate	120-51-4	-	%
Citronellol	106-22-9	-	%
Hexyl cinnam-aldehyde	101-86-0	-	%
d-Limonene	5989-27-5	< 0,2	%
Methyl heptin carbonate	111-12-6	-	%
3-Methyl-4-(2,6,6-tri-methyl-2-cyclohexen-1-yl)-3-buten-2-one	127-51-5	-	%
Oak moss extract	90028-68-5	-	%
Treemoss extract	90028-67-4	-	%

The substances listed are subject to declaration if concentration exceeds 0.001 % in leave-on and 0.01 % in rinse-off products.

Mean values are indicated according to available statistical data. All values are measured by GC-MS, 100 % method. No trace analysis is done. Values < 0.01 % are not mentioned. This is not needed since the dose of extract in the cosmetic product is normally < 0.5 %, in any case however < 5 %. In the event of changes FLAVEX will inform the costumers.

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CO_2-Extraction Authentic Quality secured by FLAVEX

CO_2 EXTRACTION

DIRECTIVES

COMMISSION DIRECTIVE 2010/69/EU

of 22 October 2010

amending the Annexes to European Parliament and Council Directive 95/2/EC on food additives other than colours and sweeteners

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives [1], and in particular Article 31 thereof,

Having regard to Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety [2], and in particular Article 53 thereof,

After consulting the Scientific Committee on Food and the European Food Safety Authority,

Whereas:

(1) European Parliament and Council Directive 95/2/EC on food additives other than colours and sweeteners [3] lays down a list of food additives that may be used in the European Union and the conditions for their use.

(2) There have been technical developments in the field of food additives since the adoption of Directive 95/2/EC. This Directive should be adapted to take into account those developments.

(3) In accordance with Article 31 of Regulation (EC) No 1333/2008 until the establishment of the Union lists of food additives as provided for in Article 30 of that Regulation is completed, the Annexes to Directive 95/2/EC shall be amended, where necessary, by measures adopted by the Commission.

(4) The following stabilisers agar (E 406), carrageenan (E 407), locust bean gum (E 410), guar gum (E 412), xanthan gum (E 415), pectins (E 440), cellulose (E 460), carboxy methyl cellulose (E 466), oxidised starch (E 1404), monostarch phosphate (E 1410), distarch phosphate (E 1412), phosphated distarch phosphate (E 1413), acetylated distarch phosphate (E 1414), acetylated starch (E 1420), acetylated distarch adipate (E 1422), hydroxyl propyl starch (E 1440), hydroxy propyl distarch phosphate (E 1442), starch sodium octenyl succinate (E 1450), acetylated oxidised starch (E 1451) and emulsifier mono- and diglycerides of fatty acids (E 471) are currently authorised under Directive 95/2/EC for a variety of uses. These food additives have been allocated an acceptable daily intake (ADI) 'not specified' by the Scientific Committee on Food (hereinafter SCF) and therefore do not present any hazard to the health of consumers. There is a technological need to extend their uses to unflavoured live fermented cream products and substitute products with a fat content of less than 20 % to ensure the stability and integrity of the emulsion. This use would benefit the consumer by providing the choice of reduced fat fermented cream products with similar properties as to the ordinary product. It is therefore appropriate to authorise this additional use.

(5) In 1990, the SCF evaluated sodium and potassium salts of lactate (E 325 and E 326), potassium acetate (E 261), sodium acetate (E 262i) and sodium hydrogen acetate (E 262ii) and came to the conclusion that they are all naturally present as constituents in food and estimates of their intake are likely to be insignificant compared to the intake from natural sources. Therefore they were all allocated a 'group ADI not specified'. Consequently, these food additives are generally permitted for use in all foodstuffs, other than those referred to in Article 2(3) of Directive 95/2/EC. There is a proposal to extend the use of these food additives into pre-packed preparations of fresh minced meat to control the growth of microbial pathogens, e.g. Listeria, E. *coli* O157. Based on this technological justification, and taking into account that this use raises no safety concern, it is appropriate to permit the additional use of these food additives in pre-packed preparations of fresh minced meat.

(6) Sorbates (E 200, E 202, E 203) and benzoates (E 210, E 211, E 212, E 213) are currently permitted as food additives under Directive 95/2/EC. An additional use as preservative of these food additives is proposed in seaweed-based fish product analogues (caviar analogues

[1] OJ L 354, 31.12.2008, p. 16.
[2] OJ L 31, 1.2.2002, p. 1.
[3] OJ L 61, 18.3.1995, p. 1.

made of seaweed) as topping on various foods in order to prevent the growth of moulds and yeasts and the formation of mycotoxins. These salts are allocated an ADI of 0-25 mg/kg bw and 0-5 mg/kg/ bw respectively. On the basis of a worst case scenario where the maximum concentrations were used, the intake estimates are very low compared to the ADI. The exposure of the consumer as a result of this use does not give rise to safety concern. It is therefore appropriate to permit the additional use of sorbates and benzoates in seaweed based fish analogue products, bearing in mind the technological justification and the fact that this new product represents a niche market.

(7) The use of sorbates (E 200, E 202, E 203) and benzoates (E 210, E 211, E 212, E 213) is requested for beers in keg to which more than 0,5 % fermentable sugars and/or fruit juices or concentrates have been added and which are directly served on draft. These beers in keg may stay connected to the beer tap for a longer time. As the connection of the keg to the tap cannot be performed under sterile conditions, microbiological contamination of the keg is possible. This is a problem for beers which still contain fermentable sugars because this may lead to the growth of hazardous microorganisms. Therefore antimicrobial agents are required in draft beers and to which fermentable sugars and/or fruit juices or concentrates have been added. From an intake point of view, the consumption on draft of such fruit beers remains marginal and the intake estimates for sorbates and benzoates, on the grounds of a 'worst case approach', should be below their respective ADIs. Therefore it is appropriate to permit the additional use of sorbates and benzoates in beer in kegs containing more than 0,5 % added fermentable sugar and/or fruit juices or concentrates.

(8) To prevent the development of moulds on citrus fruit, their post harvest treatment with pesticides such as imazalil and thiabendazole is authorised. Sorbates (E 200, E 202, E 203) could be used to replace these pesticides partly or completely for the treatment of citrus fruit. Sorbates can be applied on the surface of the unpeeled fresh citrus fruit via the authorised waxes: beeswax, candelilla wax, carnauba wax and shellac (E 901, E 902, E 903 and E 904 respectively). The exposure of the consumer to these additives due to this use is not a cause of safety concern. It is therefore appropriate to authorise its additional use.

(9) Consumers may choose to supplement their intake of some nutrients with food supplements. For that purpose, vitamin A and combinations of vitamins A and D can be added to food supplements, as defined by Directive 2002/46/EC of the European Parliament and of the Council [1]. For reasons of safe handling, vitamin A and combinations of vitamins A and D have to be formulated into preparations that may require high humidity and high temperature, in the presence of starches and sugars. Such processing may favour the development of microorganisms. In order to prevent the growth of these microorganisms, the addition of sorbates (E 200, E 202, E 203) and benzoates (E 210, E 211, E 212 and E 213) should be authorised in vitamin A and in combinations of vitamins A and D when used in food supplements supplied in dried form.

(10) Sulphur dioxide and sulphites (E 220, E 221, E 222, E 223, E 224, E 226, E 227, E 228) are food additives authorised under Directive 95/2/EC which act primarily as antimicrobial agents and controlling chemical spoilage. Nowadays, transport of fresh fruit has become very important, in particular by sea freight. Such transport may be several weeks. The use of sulphur dioxide and sulphites will protect fresh blueberries against fungi growth. The additional use of sulphur dioxide and sulphites should be authorised in order to help preserve fresh blueberries against fungi growth, bearing in mind that this is likely to represent a niche market. Taking also into consideration the sound technological reasons for including these new authorisations, the need to facilitate worldwide trade and its negligible impact in term of sulphur and sulphite intake, it is therefore appropriate to authorise the additional use of sulphur dioxide in blueberries at the concentration level indicated in the Annex to this Directive.

(11) For the production of cinnamon sticks (*Cinnamomum ceylanicum* only), also known as 'quills', the fresh peels of the inner bark of the cinnamon tree is used. The peel is exposed to microbial contamination and insect attacks, particularly under tropical and humid climatic conditions, in the producing country. Sulphur dioxide fumigation is an appropriate treatment against such microbial contamination and insect attacks. In 1994, the SCF established an ADI of 0-0,7 mg/kg bw and considered that the use of sulphur dioxide and other sulphiting agents should be limited in order to limit the occurrence of severe asthmatic reactions. Although the use of sulphur dioxide and sulphites should be limited, this specific use represents a negligible contributor in relation to the intake of sulphur dioxide and sulphites. It is therefore appropriate to authorise the additional use of sulphur dioxide and sulphites (E 220, E 221, E 222, E 223, E 224, E 226, E 227, E 228) only in this particular type of cinnamon.

(12) The European Food Safety Authority (hereinafter EFSA) assessed the information on the safety of use of nisin in an additional food category of liquid eggs, and on the safety of nisin produced using a modified production process. The EFSA confirmed in its opinion on 26 January 2006 [2] the previously established ADI of 0-0,13 mg/kg for the nisin produced using a new manufacturing and extraction process based on

[1] OJ L 183, 12.7.2002, p. 51.

[2] Scientific opinion of the Panel on Food Additives, Flavourings, Processing Aids and Material in Contact with Food on a request from the Commission related to the use of nisin (E 234) as a food additive, *The EFSA Journal* (2006) 314, p. 1.

fermentation of a sugar medium as a replacement for the traditionally milk-based medium. In this opinion, the EFSA also confirmed that the development of antibiotic resistance should not be expected from the use of nisin in food. According to the EFSA, there are no reports of nisin resistant bacterial mutants showing cross-resistance to therapeutic antibiotic. It considered that this is probably due to the differences between therapeutic antibiotics and nisin in terms of the antimicrobial mode of action. The EFSA furthermore confirmed in its opinion issued on 20 October 2006 ([1]) that the additional use of nisin in pasteurised liquid eggs under the intended conditions of use (maximum limit at 6,25 mg/l) is not a safety concern and is justified from a technological point of view to extend the shelf life of the product and also to prevent the growth of food poisoning spore-forming species, like *Bacillus cereus*, which may survive from pasteurisation treatment. It is therefore appropriate to authorise this additional use of nisin in pasteurised liquid egg.

(13) Dimethyl dicarbonate (DMDC, E 242) is a food additive permitted under Directive 95/2/EC which acts as a preservative in non-alcoholic flavoured drinks, alcohol-free wine and liquid-tea concentrate. The authorisation of this additive was decided on the basis of a positive opinion issued by the SCF in 1990 and confirmed in 1996. The SCF was unable to set an ADI, as DMDC rapidly decomposes into carbon dioxide and methanol. In 2001, the SCF was requested to investigate the safety of use of DMDC in wine. At that time the SCF considered that the formation of methanol and other reaction products, such as methylcarbamate resulting from the use of DMDC for the treatment of alcoholic beverages and wine is similar to that formed in non-alcoholic beverages, and even a heavy consumption of wine would not pose any hazard from methanol and methylcarbamate. The use of DMDC has been requested in order to prevent spoilage as a result of fermentation in unopened non-sterile filled bottles of cider, perry and fruit wines, alcohol-reduced wine, wine-based drinks and all other products covered by Council Regulation (EEC) No 1601/91 ([2]). These additional uses are not considered as being of safety concern for the consumer. Moreover, the use of DMDC could contribute to the reduction of the sulphur dioxide exposure. It is therefore appropriate to authorise the additional uses of DMDC in cider, perry and fruit wines, alcohol-reduced wine, wine-based drinks and other products covered by Regulation (EEC) No 1601/91.

(14) The EFSA assessed the information on the safety of use of extracts of rosemary when used as an antioxidant in foodstuffs. Extracts of rosemary are derived from *Rosmarinus officinalis* L. and contain several compounds which exert antioxidative functions (mainly phenolic acids, flavonoids, diterpenoids and triterpenes). Although the toxicological data on extracts of rosemary were insufficient for the EFSA to establish a numerical ADI, the EFSA considered in its opinion on 7 March 2008 ([3]) that the margin of safety was high enough to conclude that dietary exposure resulting from the proposed uses and use levels were of no safety concern. Extracts of rosemary can therefore be authorised where there is a technological justification for their use. The proposed uses of extracts of rosemary as antioxidant should be authorised and E 392 should be assigned as E number for extracts of rosemary.

(15) Whey is a by-product of cheese manufacturing. Some whey protein containing drinks have been developed in order to provide a diet sufficiently rich in proteins. To keep the proteins in suspension during the heat treatment of such drinks, the phosphates must be at levels that are higher than for normal non-alcoholic flavoured drinks. Phosphates should be authorised in whey protein containing sport drinks.

(16) Beeswax (E 901) is currently authorised as a glazing agent for use in small products of fine bakery wares coated with chocolate. This authorisation does not cover ice cream wafers that are not coated with chocolate. In addition to the fact that beeswax can be considered as an alternative to chocolate in pre-packed ice cream wafers, the coating of the wafers with beeswax would prevent the migration of water to the wafer and ensure its crunchiness and the extension of the shelf life of the product and is therefore considered technologically justified. Therefore beeswax should be authorised as a glazing agent to replace fully or partly the in-layer chocolate in pre-packed wafers containing ice-cream.

(17) The EFSA assessed the information on the safety of use of beeswax considering its additional use as a carrier of flavourings in non-alcoholic flavoured drinks. Although the available data on beeswax itself were insufficient to establish an ADI, the EFSA came to the conclusion that, due to the low toxicological profile of beeswax, the existing food uses and the proposed new use of beeswax do not raise safety concern. It is therefore appropriate to authorise this additional use of beeswax as a carrier of flavourings in non-alcoholic flavoured drinks.

([1]) Scientific opinion of the Panel on Food Additives, Flavourings, Processing Aids and Material in Contact with Food on the safety in use of nisin as a food additive in an additional category of liquid eggs and on the safety of nisin produced using a modified production process as a food additive, *The EFSA Journal* (2006) 314b, p. 1.

([2]) OJ L 149, 14.6.1991, p. 1.

([3]) Scientific opinion of the Panel on Food Additives, Flavourings, Processing Aids and Material in Contact with Food on a request from the Commission related to the use of rosemary extracts as a food additive, *The EFSA Journal* (2008) 721, p. 1.

(18) Triethyl citrate (E 1505) is currently authorised within the EU under Directive 95/2/EC as a carrier in flavourings, and in dried egg white. Its ADI was established by the SCF in 1990 at 0-20 mg/kg. An extension of use of triethyl citrate has been proposed as glazing agent of food supplement tablets. Triethyl citrate would increase the film resistance of the coating, protecting the tablet from external environment and also increase the duration of release of the product. According to the worst case scenario, this additional source of triethyl citrate intake is negligible (0,25 % of the ADI) compared to the full ADI. Therefore it is appropriate to authorise the additional use of triethyl citrate at EU level as a glazing agent for food supplement tablets.

(19) The EFSA assessed the information on the safety of polyvinyl alcohol (PVA) as a film-coating agent for food supplements and expressed its opinion on 5 December 2005 ([1]). The EFSA found the use of PVA in the coating of food supplements that are in the form of capsules and tablets to be of no safety concern. The EFSA considered that the potential human exposure to PVA under the intended conditions of use is expected to be low. PVA is reported to be minimally absorbed following oral administration. The maximum limit of use has been fixed at 18 g/kg based on the worst case scenario and on the basis of which the EFSA has undertaken its risk assessment. Due to the good adhesion qualities and film strength of polyvinyl alcohol, this new food additive is expected to play a technological role as film coating agent for food supplements, in particular in applications where moisture barrier and moisture protection properties are required. It is therefore appropriate to authorise this use at EU level. This new food additive should be assigned the E number E 1203.

(20) The EFSA assessed the information on the safety of use of six grades of polyethylene glycols (PEG 400, PEG 3000, PEG 3350, PEG 4000, PEG 6000, PEG 8000) as film coating agents for use in food supplement products and expressed its opinion on 28 November 2006 ([2]). The EFSA found the use of these grades of polyethylene glycol as a glazing agent in film-coating formulations for food supplement tablets and capsules under the intended conditions of use of no safety concern. The EFSA has also taken into consideration in its risk assessment the additional source of exposure to these PEGs originating from the use of pharmaceutical products and considered that only a limited additional intake may result from the already approved use of PEG 6000 as carrier for sweeteners, as well as from the use of PEG in food contact materials. It is therefore appropriate to authorise this new use at EU level. In addition, due to the limited intake from PEG 6000 as carrier of sweeteners and its similar toxicological profile with respect to the other PEG grades (the six PEGs have been allocated a group tolerable daily intake (TDI), it is also appropriate to authorise the use of the PEGs evaluated by the EFSA as an alternatives to PEG 6000 as carrier of sweeteners. All these PEGs should be assigned E 1521 as E number.

(21) The EFSA assessed the information on the safety of use of cassia gum as a new food additive acting as gelling agent and thickener and expressed its opinion on 26 September 2006 ([3]). The EFSA found the use of cassia gum as indicated under the conditions specified raised no safety concern. Although the EFSA considered the available toxicological data on cassia gum as insufficient to derive an ADI, they did not consider that the existing data gave cause for concern. In particular the EFSA highlighted the specific low absorption of cassia gum and the fact that, if hydrolysed at all, cassia gum would be degraded to compounds that will enter the normal metabolic pathways. There is a technological justification for the use of cassia gum through its synergistic gelling effects when added to other regular food gums. It is therefore appropriate to authorise these uses at EU level and to assign E 427 as E number for cassia gum.

(22) The EFSA evaluated the safety of neotame as a flavour enhancer and expressed its opinion on 27 September 2007 ([4]). The EFSA concluded that neotame is of no safety concern with respect to the proposed uses as a flavour enhancer and established an ADI of 0-2 mg/kg bw/day. Therefore it is necessary to authorise the use of neotame as a flavour enhancer.

(23) The EFSA assessed the information on the safety of use of L-cysteine (E 920) in certain foodstuffs intended for infants and young children. The EFSA concluded in

([1]) Scientific opinion of the Panel on Food Additives, Flavourings, Processing Aids and Material in Contact with Food on a request from the Commission related to the use of polyvinyl alcohol as a coating agent for food supplement, *The EFSA Journal* (2005) 294, p. 1.

([2]) Scientific opinion of the Panel on Food Additives, Flavourings, Processing Aids and Material in Contact with Food on a request from the Commission related to the use of polyethylene glycol (PEG) as a film coating agent for use in food supplement products, *The EFSA Journal* (2006) 414, p. 1.

([3]) Scientific opinion of the Panel on Food Additives, Flavourings, Processing Aids and Material in Contact with Food on a request from the Commission related to an application on the use of cassia gum as a food additive, *The EFSA Journal* (2006) 389, p. 1.

([4]) Scientific opinion of the Panel on Food Additives, Flavourings, Processing Aids and Material in Contact with Food on a request from the Commission on neotame as a sweetener and flavour enhancer, *The EFSA Journal* (2007) 581, p. 1.

its opinion on 26 September 2006 [1] that its proposed use in processed cereal-based foods and foods (specifically baby biscuits) for infants and young children is of no safety concern. Biscuits for infants and young children are required to have a suitable composition, including a controlled content of sugar and fat. However, biscuits with a low fat content have increased brittleness with an associated risk of choking and suffocation due to the biscuit breaking in the child's mouth. The function of the L-cysteine is to act as a dough improver to control the texture of the final product. It is therefore appropriate to authorise the use of L-cysteine in biscuits for infants and young children at EU level.

(24) EFSA assessed the safety of use of an enzyme preparation based on thrombin with fibrinogen derived from cattle and/or pigs as a food additive for reconstituting food and concluded in its opinion on 26 April 2005 that this use of the enzyme preparation when produced as outlined in the opinion is of no safety concern [2]. However, the European Parliament in its Resolution of 19 May 2010 on the draft Commission Directive amending the Annexes to the European Parliament and Council Directive 95/2/EC on food additives other than colours and sweeteners, considered that the inclusion in Annex IV to Directive 95/2/EC of this enzyme preparation as a food additive for reconstituting food was not compatible with the aim and content of Regulation (EC) No 1333/2008, as it does not meet the general criteria of Article 6 of Regulation (EC) No 1333/2008, especially in paragraph 1(c) of Article 6.

(25) Commission Decision 2004/374/EC [3] suspended the placing on the market and import of jelly mini-cups containing gel-forming food additives derived from seaweed and certain gums (E 400, E 401, E 402, E 403, E 404, E 405, E 406, E 407, E 407a, E 410, E 412, E 413, E 414, E 415, E 417, E 418) due to the risk of choking posed by these products. Directive 95/2/EC was amended accordingly by Directive 2006/52/EC of the European Parliament and of the Council [4]. Commission Decision 2004/374/EC should therefore be repealed as its provisions have been included in Directive 95/2/EC.

(26) The measures provided for in this Directive are in accordance with the opinion of the Standing Committee on the Food Chain and Animal Health, and neither the European Parliament nor the Council has opposed them,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Annexes II to VI to Directive 95/2/EC are amended in accordance with the Annex to this Directive.

Article 2

1. Member States shall adopt and publish, by 31 March 2011 at the latest, the laws, regulations and administrative provisions necessary to comply with Article 1 of this Directive. They shall forthwith communicate to the Commission the text of those provisions.

They shall apply those provisions from 1 April 2011 at the latest.

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

Article 3

Commission Decision 2004/374/EC is repealed.

Article 4

This Directive shall enter into force on the twentieth day following its publication in the *Official Journal of the European Union*.

Article 5

This Directive is addressed to the Member States.

Done at Brussels, 22 October 2010.

For the Commission
The President
José Manuel BARROSO

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[1] Scientific opinion of the Panel on Food Additives, Flavourings, Processing Aids and Material in Contact with Food on a request from the Commission related to the use of L-cysteine in foods intended for infants and young children, *The EFSA Journal* (2006) 390, p. 1.

[2] Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to the use of an enzyme preparation based on thrombin: fibrinogen derived from cattle and/or pigs as a food additive for reconstituting food, *The EFSA Journal* (2005) 214, p. 1.

[3] OJ L 118, 23.4.2004, p. 70.

[4] OJ L 204, 26.7.2006, p. 10.

ANNEX

Annexes II to VI to Directive 95/2/EC are amended as follows:

(1) Annex II is amended as follows:

(a) the entry concerning 'Pre-packed preparations of fresh minced meat' is replaced by the following:

'Pre-packed preparations of fresh minced meat	E 261	Potassium acetate	*quantum satis*'
	E 262i	Sodium acetate	
	E 262ii	Sodium hydrogen acetate	
	E 300	Ascorbic acid	
	E 301	Sodium ascorbate	
	E 302	Calcium ascorbate	
	E 325	Sodium lactate	
	E 326	Potassium lactate	
	E 330	Citric acid	
	E 331	Sodium citrates	
	E 332	Potassium citrates	
	E 333	Calcium citrates	

(b) at the end of the Annex, the following entry is added:

'Unflavoured live fermented cream products and substitute products with a fat content of less than 20 %	E 406	Agar	*quantum satis*'
	E 407	Carrageenan	
	E 410	Locust bean gum	
	E 412	Guar gum	
	E 415	Xanthan gum	
	E 440	Pectins	
	E 460	Cellulose	
	E 466	Carboxy methyl cellulose	
	E 471	Mono- and diglycerides of fatty acids	
	E 1404	Oxidised starch	
	E 1410	Monostarch phosphate	
	E 1412	Distarch phosphate	
	E 1413	Phosphated distarch phosphate	
	E 1414	Acetylated distarch phosphate	
	E 1420	Acetylated starch	
	E 1422	Acetylated distarch adipate	
	E 1440	Hydroxyl propyl starch	

	E 1442	Hydroxy propyl distarch phosphate	
	E 1450	Starch sodium octenyl succinate	
	E 1451	Acetylated oxidised starch	

(2) Annex III is amended as follows:

(a) at the end of Part A, the following entries are added:

'Seaweed-based fish analogue products	1 000	500				
Beer in kegs containing more than 0,5 % added fermentable sugar and/or fruit juices or concentrates	200	200		400		
Unpeeled fresh citrus fruit (surface treatment only)	20					
Food supplements as defined in Directive 2002/46/EC supplied in dried form containing preparations of vitamin A and of combinations of vitamin A and D				1 000 in the product ready for consumption'		

(b) at the end of Part B, the following entries are added:

'Blueberries (*Vaccinium corymbosum* only)	10
Cinnamon (*Cinnamomum ceylanicum* only)	150'

(c) Part C is amended as follows:

(i) the entry concerning the additive E 234 is replaced by the following:

'E 234	Nisin (*)	Semolina and tapioca puddings and similar products	3 mg/kg
		Ripened cheese and processed cheese	12,5 mg/kg
		Clotted cream	10 mg/kg
		Mascarpone	10 mg/kg
		Pasteurised liquid egg (white, yolk or whole egg)	6,25 mg/l

(*) This substance may be present in certain cheeses as a result of fermentation process.'

(ii) the entry concerning the additive E 242 is replaced by the following:

'E 242	Dimethyl dicarbonate	Non-alcoholic flavoured drinks Alcohol-free wine Liquid-tea concentrate	250 mg/l ingoing amount, residues not detectable
		Cider, perry, fruit wines Alcohol-reduced wine Wine-based drinks and products covered by Regulation (EEC) No 1601/91	250 mg/l ingoing amount, residues not detectable'

(d) in Part D the following entry is inserted after the entry concerning additive E 316:

'E 392	Extracts of rosemary	Vegetable oils (excluding virgin oils and olive oils) and fat where content of polyunsaturated fatty acids is higher than 15 % w/w of the total fatty acid, for the use in non heat treated food products	30 mg/kg (expressed as the sum of carnosol and carnosic acid) Expressed on fat basis
		Fish oils and algal oil	50 mg/kg (expressed as the sum of carnosol and carnosic acid) Expressed on fat basis
		Lard, beef, poultry, sheep and porcine fat Fats and oils for the professional manufacture of heat-treated foodstuffs Frying oil and frying fat, excluding olive oil and olive pomace oil Snack foods (snack based on cereals, potatoes or starch)	
		Sauces	100 mg/kg (expressed as the sum of carnosol and carnosic acid] Expressed on fat basis
		Fine bakery wares	200 mg/kg (expressed as the sum of carnosol and carnosic acid] Expressed on fat basis
		Food supplements as defined in Directive 2002/46/EC	400 mg/kg (expressed as the sum of carnosol and carnosic acid)
		Dehydrated potatoes Egg products Chewing gum	200 mg/kg (expressed as the sum of carnosol and carnosic acid)
		Milk powder for vending machines Seasoning and condiments Processed nuts	200 mg/kg (expressed as the sum of carnosol and carnosic acid) Expressed on fat basis
		Dehydrated soups and broths	50 mg/kg (expressed as the sum of carnosol and carnosic acid)
		Dehydrated meat	150 mg/kg (expressed as the sum of carnosol and carnosic acid)
		Meat and fish products, excluding dehydrated meat and dried sausage	150 mg/kg (expressed as the sum of carnosol and carnosic acid) Expressed on fat basis
		Dried sausage	100 mg/kg (expressed as the sum of carnosol and carnosic acid)
		Flavourings	1 000 mg/kg (expressed as the sum of carnosol and carnosic acid)
		Dried milk for the manufacturing of ice cream	30 mg/kg (expressed as the sum of carnosol and carnosic acid)'

(3) Annex IV is amended as follows:

(a) in the entry concerning additives E 338, E 339, E 340, E 341, E 343, E 450, E 451 and E 452, the following row is inserted after the row concerning 'vegetable protein drinks':

		'Whey protein containing sport drinks	4 g/kg'

(b) the following entry is inserted before the entry concerning additives E 432, E 433, E 434, E 435 and E 436:

'E 427	Cassia gum	Edible ices	2 500 mg/kg
		Fermented milk products with the exception of unflavoured live fermented milk products	
		Dairy-based dessert and similar products	
		Filling, topping and coating for fine bakery wares and dessert	
		Processed cheese	
		Sauces and salads dressing	
		Dehydrated soups and broths	
		Heat-treated meat products	1 500 mg/kg'

(c) in the entry for E 901, E 902, and E 904, in the third column, under the use 'As glazing agent only for', the following entry is added:

		'— Pre-packed wafers containing ice cream (only for E 901)	*quantum satis*'

(d) in the entry for E 901, E 902, and E 904, in the third column, below the use as 'Peaches and pineapples (surface treatment only)', the following entry is added:

		'Flavourings in non-alcoholic flavoured drinks (only for E 901)	0,2 g/kg in the flavoured drinks'

(e) the following entry is inserted after the entry concerning the additive E 959:

'E 961	Neotame	Water-based flavoured drinks, energy-reduced or with no added sugar	2 mg/l as flavour enhancer
		Milk- and milk-derivative-based or fruit-juice-based drinks, energy-reduced or with no added sugar	2 mg/l as flavour enhancer
		"Snacks": certain flavours of ready-to-eat, pre-packed, dry, savoury starch products and coated nuts	2 mg/kg as flavour enhancer
		Starch-based confectionery, energy-reduced or with no added sugar	3 mg/kg as flavour enhancer
		Breath-freshening micro-sweets, with no added sugar	3 mg/kg as flavour enhancer
		Strongly flavoured throat pastilles with no added sugar	3 mg/kg as flavour enhancer
		Chewing gum with added sugar	3 mg/kg as flavour enhancer
		Energy-reduced jams, jellies and marmalades	2 mg/kg as flavour enhancer

		Sauces	2 mg/kg as flavour enhancer
		Food supplements as defined in Directive 2002/46/EC supplied in a liquid form	2 mg/kg as flavour enhancer
		Food supplements as defined in Directive 2002/46/EC supplied in a solid form	2 mg/kg as flavour enhancer
		Food supplements as defined in Directive 2002/46/EC based on vitamins and/or mineral elements and supplied in a syrup-type or non-chewable form	2 mg/kg as flavour enhancer'

(f) the following entry is inserted after the entry concerning additive E 1202:

'E 1203	Polyvinyl alcohol	Food supplements as defined in Directive 2002/46/EC in capsule and tablet form	18 g/kg'

(g) after the entry concerning the additive E 1202, the entry concerning only the food additive E 1505 is replaced by the following:

'E 1505	Triethyl citrate	Food supplements as defined in Directive 2002/46/EC in capsule and tablet form	3,5 g/kg
		Dried egg white	*quantum satis*'

(h) the following entry is inserted after the entry concerning the additive E 1452:

'E 1521	Polyethylene glycol	Food supplements as defined in Directive 2002/46/EC in capsule and tablet form	10 g/kg'

(4) In Annex V, the entry concerning the additive 'Polyethyleneglycol 6000' is replaced by the following:

'E 1521	Polyethylene glycol	Sweeteners'

(5) In Part 3 of Annex VI, the following entry is added after the entry concerning additive E 526:

'E 920	L-cysteine	Biscuits for infants and young children	1 g/kg'

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: June 14, 2013

SUBJECT: Updated Concentration of Use by FDA Product Category: Rosemary-Derived Ingredients (added rosemary leaf oil)

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Concentration of Use by FDA Product Category

Rosmarinus Officinalis (Rosemary) Extract
Rosmarinus Officinalis (Rosemary) Flower Extract
Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Extract
Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Water
Rosmarinus Officinalis (Rosemary) Flower Wax
Rosmarinus Officinalis (Rosemary) Leaf
Rosmarinus Officinalis (Rosemary) Leaf Extract
Rosmarinus Officinalis (Rosemary) Leaf Oil
Rosmarinus Officinalis (Rosemary) Leaf Powder
Rosmarinus Officinalis (Rosemary) Leaf Water
Rosmarinus Officinalis (Rosemary) Water

Ingredient	FDA Code†	Product Category	Maximum Concentration of Use
Rosmarinus Officinalis (Rosemary) Extract	03C	Eye shadow	0.01%
Rosmarinus Officinalis (Rosemary) Extract	03D	Eye lotion	0.01%
Rosmarinus Officinalis (Rosemary) Extract	03F	Mascara	0.05%
Rosmarinus Officinalis (Rosemary) Extract	05A	Hair conditioners	0.00004%
Rosmarinus Officinalis (Rosemary) Extract	05F	Shampoos (noncoloring)	0.00004-0.003%
Rosmarinus Officinalis (Rosemary) Extract	05G	Tonics, dressings and other hair grooming aids	0.001%
Rosmarinus Officinalis (Rosemary) Extract	07B	Face powders	0.05%
Rosmarinus Officinalis (Rosemary) Extract	07C	Foundations	0.051%
Rosmarinus Officinalis (Rosemary) Extract	07E	Lipstick	0.011%
Rosmarinus Officinalis (Rosemary) Extract	10A	Bath soaps and detergents	0.0005-0.16%
Rosmarinus Officinalis (Rosemary) Extract	10B	Deodorants not spray aerosol	 0.0098% 0.0098-0.012%

Rosmarinus Officinalis (Rosemary) Extract	11E	Shaving cream (aerosol, brushless and lather)	0.009%
Rosmarinus Officinalis (Rosemary) Extract	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.04%
Rosmarinus Officinalis (Rosemary) Extract	12C	Face and neck products not spray	0.05%
Rosmarinus Officinalis (Rosemary) Extract	12D	Body and hand products not spray	0.00096%
Rosmarinus Officinalis (Rosemary) Extract	13A	Suntan products	0.01%
Rosmarinus Officinalis (Rosemary) Extract	13B	Indoor tanning preparations	0.00096%
Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Extract	10B	Deodorants not spray	0.0024%
Rosmarinus Officinalis (Rosemary) Leaf	05G	Tonics, dressings and other hair grooming aids	0.002%
Rosmarinus Officinalis (Rosemary) Leaf Extract	01B	Baby lotions, oils and creams	0.012%
Rosmarinus Officinalis (Rosemary) Leaf Extract	02A	Bath oils tablets and salts	0.0002%
Rosmarinus Officinalis (Rosemary) Leaf Extract	02B	Bubble baths	0.0004%
Rosmarinus Officinalis (Rosemary) Leaf Extract	02D	Other bath preparations	0.04%
Rosmarinus Officinalis (Rosemary) Leaf Extract	03B	Eye liner	0.02-0.063%
Rosmarinus Officinalis (Rosemary) Leaf Extract	03C	Eye shadow	0.13-3%
Rosmarinus Officinalis (Rosemary) Leaf Extract	03D	Eye lotion	0.002-0.1%
Rosmarinus Officinalis (Rosemary) Leaf Extract	04A	Colognes and toilet waters	0.001%

Rosmarinus Officinalis (Rosemary) Leaf Extract	04E	Other fragrance preparations	0.5%
Rosmarinus Officinalis (Rosemary) Leaf Extract	05A	Hair conditioners	0.0001-0.11%
Rosmarinus Officinalis (Rosemary) Leaf Extract	05B	Hair sprays aerosol pump spray	 0.0016% 0.0001-0.005%
Rosmarinus Officinalis (Rosemary) Leaf Extract	05E	Rinses (noncoloring)	0.0002%
Rosmarinus Officinalis (Rosemary) Leaf Extract	05F	Shampoos	0.00005-0.11%
Rosmarinus Officinalis (Rosemary) Leaf Extract	05G	Tonics dressings and other hair grooming aids spray	0.00002-0.5% 0.0004%
Rosmarinus Officinalis (Rosemary) Leaf Extract	05I	Other hair preparations (non-coloring)	0.00001%
Rosmarinus Officinalis (Rosemary) Leaf Extract	06G	Hair bleaches	0.04%
Rosmarinus Officinalis (Rosemary) Leaf Extract	07B	Face powders	0.0002%
Rosmarinus Officinalis (Rosemary) Leaf Extract	07C	Foundations	0.001-0.0015%
Rosmarinus Officinalis (Rosemary) Leaf Extract	07D	Leg and body paints	0.014%
Rosmarinus Officinalis (Rosemary) Leaf Extract	07E	Lipstick	0.00001-0.009%
Rosmarinus Officinalis (Rosemary) Leaf Extract	07F	Makeup bases	0.001%
Rosmarinus Officinalis (Rosemary) Leaf Extract	08B	Cuticle softeners	0.005%
Rosmarinus Officinalis (Rosemary) Leaf Extract	08G	Other manicuring preparations	0.053%
Rosmarinus Officinalis (Rosemary) Leaf Extract	10A	Bath soaps and detergents	0.001-3%
Rosmarinus Officinalis (Rosemary) Leaf Extract	10E	Other personal cleanliness products	0.002-0.02%

Rosmarinus Officinalis (Rosemary) Leaf Extract	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.00001-0.38%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12B	Depilatories	0.0002-0.01%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12C	Face and neck products not spray	 0.00004-0.1%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12D	Body and hand products not spray spray	 0.0005-10% 0.002%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12F	Moisturizing products not spray	 0.0013-0.5%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12G	Night products not spray	 0.012%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12H	Paste masks and mud packs	0.001-0.06%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12I	Skin fresheners	0.4%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12J	Other skin care preparations	0.005-0.013%
Rosmarinus Officinalis (Rosemary) Leaf Extract	13A	Suntan products not spray	 0.05%
Rosmarinus Officinalis (Rosemary) Leaf Oil	02A	Bath oils, tablets and salts	0.5-0.97%
Rosmarinus Officinalis (Rosemary) Leaf Oil	04C	Powders (dusting and talcum)	0.0003%
Rosmarinus Officinalis (Rosemary) Leaf Oil	05A	Hair conditioners	0.05-0.12%
Rosmarinus Officinalis (Rosemary) Leaf Oil	05B	Hair sprays aerosol	 0.007%
Rosmarinus Officinalis (Rosemary) Leaf Oil	05E	Rinses (noncoloring)	0.04%

Rosmarinus Officinalis (Rosemary) Leaf Oil	05F	Shampoos (noncoloring)	0.00001-0.32%
Rosmarinus Officinalis (Rosemary) Leaf Oil	05G	Tonics, dressings and other hair grooming aids	0.006-1.5%
Rosmarinus Officinalis (Rosemary) Leaf Oil	07C	Foundations	0.02%
Rosmarinus Officinalis (Rosemary) Leaf Oil	07E	Lipstick	0.008%
Rosmarinus Officinalis (Rosemary) Leaf Oil	07F	Makeup bases	0.0036%
Rosmarinus Officinalis (Rosemary) Leaf Oil	10A	Bath soaps and detergents	0.0002-0.61%
Rosmarinus Officinalis (Rosemary) Leaf Oil	11A	Aftershave lotions	0.0012%
Rosmarinus Officinalis (Rosemary) Leaf Oil	11E	Shaving cream (aerosol, brushless and lather)	0.0039%
Rosmarinus Officinalis (Rosemary) Leaf Oil	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.015-0.04%
Rosmarinus Officinalis (Rosemary) Leaf Oil	12C	Face and neck products not spray spray	 0.032-0.55% 0.011%
Rosmarinus Officinalis (Rosemary) Leaf Oil	12D	Body and hand products not spray spray	 0.002-1.5% 1.5%
Rosmarinus Officinalis (Rosemary) Leaf Oil	12F	Moisturizing products not spray	0.005%
Rosmarinus Officinalis (Rosemary) Leaf Oil	12H	Pastes masks and mud packs	0.01%
Rosmarinus Officinalis (Rosemary) Leaf Powder	05A	Hair conditioners	0.05%
Rosmarinus Officinalis (Rosemary) Leaf Water	03D	Eye lotion	0.00016%

Rosmarinus Officinalis (Rosemary) Leaf Water	03F	Mascara	0.000069%
Rosmarinus Officinalis (Rosemary) Leaf Water	05A	Hair conditioners	0.00022%
Rosmarinus Officinalis (Rosemary) Leaf Water	05F	Shampoos (noncoloring)	0.00019-0.25%
Rosmarinus Officinalis (Rosemary) Leaf Water	05G	Tonics, dressings and other hair grooming aids	1%
Rosmarinus Officinalis (Rosemary) Leaf Water	07C	Foundations	0.00009%
Rosmarinus Officinalis (Rosemary) Leaf Water	07E	Lipstick	0.005%
Rosmarinus Officinalis (Rosemary) Leaf Water	11E	Shaving cream (aerosol, brushless and lather)	0.00015-0.07%
Rosmarinus Officinalis (Rosemary) Leaf Water	12C	Face and neck products not spray	0.36%
Rosmarinus Officinalis (Rosemary) Leaf Water	12D	Body and hand products not spray	0.00015-0.002%

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

†Product category codes used by FDA

Information collected in 2013
Table prepared: June 5, 2013
Updated June 13, 2013: added Rosmarinus Officinalis (Rosemary) Leaf Oil

Personal Care Products Council
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TO: Lillian Gill, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: July 29, 2013

SUBJECT: Concentration of Use by FDA Product Category: Rosmarinic Acid

Rosmarinic Acid was included in a concentration of use survey. No uses were reported.

Memorandum

TO: Lillian Gill, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: July 9, 2013

SUBJECT: Comments on the Scientific Literature Review (SLR) on *Rosmarinus officinalis* (Rosemary)-Derived Ingredients

The Council does not have any suppliers listed for Rosmarinus Officinalis (Rosemary) Water.

Key Issue

Please explain why Rosmarinic Acid was included as an ingredient in this report, while other constituents of rosemary-derived ingredients that are also in the Dictionary, such as Carnosic Acid, Oleanolic Acid, Ursolic Acid, Betulin, Luteolin, Diosmetin, Apigenin, Caffeic Acid and Chlorogenic Acids are not included in the report. Perhaps the CIR Expert Panel should have a discussion concerning the inclusion of plant components in reports concerning plant extracts. For licorice, the CIR Expert Panel decided to prepare a report on the components before they considered the safety of the complex mixtures of the plant extracts. As the antioxidant-containing rosemary extracts appear to be normalized to carnosol and Carnosic Acid, perhaps the CIR Expert may consider having a report on diterpenes before the report on rosemary-derived ingredients is completed.

p.1 - Rather than a subsection called Geographical Origin, it would be helpful to include a section with general information about the plant. This section would include information such as a description of the plant, geographical origin, other names (genus species as well as common names), plant family and other general information, e.g., this an herbaceous flowering plant that is commonly used to flavor foods.

Additional Comments

p.2 - If it is not stated earlier, the plant family that includes rosemary should be stated.

p.2 - Please indicate that the allergenic compounds listed separately are all fragrance ingredients required to be listed on the label of products in Europe if they exceed certain limits.

p.3, 7, 10, 39 reference 4 - If the PDR for Herbal Medicines is going to be cited, a more recent edition should be obtained (the 4th edition was published in 2007). As it gets completed, the USP Herbal Medicines Compendium available at http://www.usp.org/around-world/herbal-medicines-compendium might be a better reference (it

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does not appear to include rosemary) than the 1998 1st edition of the PDR for Herbal Medicines.

p. 4, 5 - It would be helpful if the Dermal section and the Percutaneous Absorption section were presented together. The Dermal section summarizes *in vivo* studies, while the Percutaneous Absorption section summarizes *in vitro* studies, which should predict the results *in vivo*. It would be easier to compare the two types of studies if they were presented together.

p.4 - Based on searching PubMed ("glucuronized" (26 hits), "glucuronidated" (816 hits)), glucuronidated appears to be the term most commonly used to describe compounds conjugated with glucuronic acid.

p.5, 10 - Did the investigators that studied the distribution of Rosmarinic Acid really follow the compound itself, or did they just measure radioactivity?

p.5 - Please correct "5 days be gavage"

p.6 - What was measured in the clinical study of Rosmarinic Acid (reference 45)?

p.6 - What was the extraction solvent for the extract studied in reference 47? How did the results of the extract compare with the results of the individual constituents that were tested?

p.6 - In the paragraph on Immunologic effects, please provide some indication of the concentrations that were tested.

p.6 - Did reference 50 include an ethanol exposed control group?

p.7-8 - The heading "Estrogenic Activity" is not appropriate as the studies summarized in this section indicate that rosemary preparations increased the metabolism of estrogen compounds and had anti-estrogenic activity.

p.8, 11 - The material that was tested at 1500 mg/kg bw/day in a micronucleus assay was an extract from which the volatile oil was removed (see Table 11). Therefore, it is not correct to describe this material as "an oil that was extracted using absolute ethanol" - this material was an extract not an essential oil.

p.9 - In the Case Reports section, the type of tests in which carnosol was positive is not clear.

p.9 - As the rosemary-derived ingredients included in this report are complex mixtures, it is not clear what the request for "toxicokinetics data on Rosmarinus officinalis (rosemary) ingredients means". For which components of these ingredients are data needed?

p.11 - The Summary includes too many details on the effects of rosemary-derived ingredients on estrogen metabolism.

p.11 - Please correct "Rosmarinc acid, dosed by gavage..." (it was the hamsters that were actually dosed)

p.24, Table 4 - Carnosol is listed with triterpene acids under "Plant part not specified" and under diterpenes under "Leaf". Which is correct?

p.25, Table 6 (and other tables) - Is it correct that extraction solvents used were partially deodorized ethanol and deodorized ethanol (as it is stated)? Or was rosemary extracted with ethanol and then the extracts were partially or completely deodorized?

p.26, Table 7 - If IFRA and/or the European Union has limits on the monoterpene ingredients, it would be helpful to include them in this table.