Safety Assessment of Chamomilla Recutita-Derived Ingredients as Used in Cosmetics

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ABSTRACT: The *Chamomilla recutita*-derived ingredients function mostly as fragrance ingredients and skin conditioning agents in cosmetic products. These ingredients are used at concentrations up to 0.5% (chamomilla recutita (matricaria) flower) in cosmetic products. Because formulations may contain more than one botanical ingredient, caution was urged to avoid reaching levels of toxicity for constituents. The Expert Panel concluded that the *Chamomilla recutita* flower-derived ingredients are safe in the present practices of use and concentration in cosmetics, when formulated to be non-sensitizing. However, the Panel determined that the available data are insufficient to make a determination that ingredients derived from chamomilla recutita leaf and stem, and the whole plant are safe under the intended conditions of use in cosmetics and that chemical composition data on these ingredients are needed.

INTRODUCTION

This report presents information relevant to evaluating the safety of the following 11 chamomile (German chamomile [*Chamomilla recutita* (*matricaria*)])-derived ingredients as used in cosmetics: chamomilla recutita (matricaria) flower, chamomilla recutita (matricaria) flower extract, chamomilla recutita (matricaria) flower powder, chamomilla recutita (matricaria) flower water, chamomilla recutita (matricaria) flower oil, chamomilla recutita (matricaria) extract, chamomilla recutita (matricaria) flower/leaf extract, chamomilla recutita (matricaria) flower/leaf/stem extract, chamomilla recutita (matricaria) flower/leaf/stem water, chamomilla recutita (matricaria) leaf extract, and chamomilla recutita (matricaria) oil. These ingredients function mostly as fragrance ingredients and skin conditioning agents in cosmetic products. In addition to being a skin conditioning agent, chamomilla recutita (matricaria) flower/leaf/stem extract also functions as a flavoring agent and an oral care agent. Chamomilla recutita (matricaria) leaf/stem extract functions as a cosmetic biocide only. It should be noted that chamomilla recutita (matricaria) flower oil is also known as German chamomile oil, a term which is used frequently in the published literature.[1]

Azulene has been identified as a component of chamomilla recutita (matricaria) flower oil. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) has concluded that the available data are insufficient to support the safety of azulene (not to be confused with guaiazulene) for use in cosmetic products.[2] Because chamomilla recutita (matricaria) flower oil may contain (-)-α-bisabolol at concentrations as high as 41.45%, safety test data from the 1999 CIR final report on bisabolol are included in Table 1.[3] The Panel concluded, in 1999, that bisabolol is safe as used in cosmetic products; reported use concentrations ranged from 0.001% to 1%.

CHEMISTRY

The plant source of the ingredients reviewed in this safety assessment is *Matricaria chamomilla* L. [Asteraceae]. Compositae family is the previous or historical name for the Asteraceae family. *Chamomilla recutita* and *Matricaria recutita* are synonyms for *Matricaria chamomilla*.[4] The definitions of 11 chamomile ingredients presented in this safety assessment are included in Table 2. The structural formulas for constituents of chamomilla recutita (matricaria) flower oil and chamomilla recutita (matricaria) flower extract are included in Figure 1.

Physical and Chemical Properties

Chemical and physical properties of chamomilla recutita (matricaria) flower oil are included in Table 3. Information on the other 10 ingredients was not found, nor was unpublished information provided.

Method of Manufacture

Chamomilla Recutita (Matricaria) Flower Oil

Chamomilla recutita (matricaria) flower oil is produced via steam distillation of chamomile (*Chamomilla recutita*) flowers.[5,6] According to another publication, chamomilla recutita (matricaria) flower oil is prepared by steam distillation of the flowers and stalks of *Chamomilla recutita* (*Matricaria*).[7] Whether the difference in source material influences the composition of the cosmetic ingredient is unknown.

Chamomilla Recutita (Matricaria) Flower Extract

One of the trade name mixtures associated with chamomilla recutita (matricaria) flower extract has the INCI name, mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract (see Table 4). This trade name mixture is manufactured by prolonged maceration of flowers in a mixture of mineral oil and apricot kernel oil.[8] Another trade name mixture associated with chamomilla recutita (matricaria) flower extract has the INCI name, propylene glycol (and) water (and) chamomilla recutita (matricaria) flower extract (see Table 4). This trade name mixture is manufactured by hydroglycolic extraction.[9]

Composition/Impurities

Composition data (contents of the mixture, not the plant-derived ingredient) on various trade name mixtures containing *Chamomilla recutita (Matricaria)* ingredients are summarized in Table 4.[10]

Data on the composition (contents of the plant-derived ingredient) of chamomilla recutita (matricaria) flower extract, chamomilla recutita (matricaria) flower oil, and chamomilla recutita (matricaria) flower are included in Table 5. Additional information relating to composition is included below.

Chamomilla Recutita (Matricaria)

The chamomile species *Chamomilla recutita* may be classified into 4 different chemotypes, depending on the main constituent of the essential oil:[11] bisabolol, bisabolol oxide A, bisabolol oxide B, and bisabolone oxide A. A characteristic constituent of chamomile flowers is the essential oil, which contains bisabolol, matricine, or its artifact (chamazulene), *trans* -farnesene, and *cis*- as well as trans-*en*-*in*-dicycloether as typical components. Other than the coumarins herniarin and umbelliferone, flavonoids are the main hydrophilic constituents of the flower. Pectin-like polysaccharides with a main chain of α-1→4-linked polygalacturonic acid and a highly branched polysaccharide with β-1→4-linked xylose are also present.

The occurrence of formaldehyde in intact *Chamomilla recutita* (*Matricaria*) plants was evaluated. Wild *Chamomilla recutita* (*Matricaria*) and 2 varieties of this plant, BK-2 and *Degumil*, grown in Hungary were studied.[12] The BK-2 and *Degumil* varieties were grown in central Hungary, whereas, the wild type was grown in southern Hungary. Formaldehyde (HCHO) in dimedone adduct form (formaldemethone) was identified and quantified using automatic overpressured layer chromatography (OPLC). Plant samples were frozen, powdered, and treated with a 0.2% solution of dimedone in methanol. Each plant part (root, shoot, or inflorescence) suspension was then centrifuged and the supernatant was used for OPLC. The inflorescence (≈ 6.5 µg HCHO/g) and root (≈ 7 µg HCHO/g) samples of the intact, soil-grown *Degumil* variety contained the greatest quantity of HCHO, followed by the shoots and inflorescence of the cultivated BK-2 and *Degumil* varieties. The wild type contained similar amounts of HCHO in its inflorescence (≈ 5µg HCHO/g) and shoots (5µg HCHO/g). The amount of HCHO bound by the dimedone reagent increased as the concentration of dimedone increased, until a maximum was reached.

A study identified the following impurities in dry chamomile (*Chamomilla recutita*) grown in Croatia: lead and cadmium heavy metals, and the herbicides linuron, fluazifop-p-butyl, and cycloxydim.[14] Cadmium and all 3 herbicide residues in dried samples of industrially grown dry chamomile were found to be above the suggested and accepted tolerance values. The source of this information is an abstract of a study in Croatian.

Influence of Plant Line

A study was performed to characterizethe individual variability of components in 10 selected lines (U2, U5, U7, U10, U14, S7, S10, S17, S22, and S24) that originate from the chamomile (*Chamomilla recutita*) plant population.[13] Seedlings were planted in Poland in October of 2000 and flower heads were harvested during the following year. For the 10 chamomile lines investigated, the essential oil content ranged from 0.25 to 0.55%. Of the 60 components of essential oil detected using gas chromatography, 19 were identified. The major components were: bisabolol oxide B (24.08% to 33.75%), bisabolol oxide A (5.75% to 10.92%), chamazulene (30.42%), farnesene (3.89% to 5.90%), spathulenol (3% to 4.90%), and spiroether (12.63% to 19.95%). Polyacetylene – spiroether is the component of chamomile essential oil that has anti-inflammatory activity. Concentration ranges for 2 other sesquiterpenes (minor components) were α-bisabolone oxide (2.53% to 7.52%) and α-bisabolol (0.12% to 0.73%). The monoterpenes sabinene, limonene, and cineol were present in small amounts, and only traces of α-pinene, *p*-cymene, and γ-terpinene were detected.

Influence of Drying Process

In the post-harvest processing of *Chamomilla recutita*, drying is an important process for preserving plant material, because it inhibits enzymatic degradation and limits microbial growth.[15] The phenolic content of *Chamomilla recutita* consists of the flavonoids, flavone glycosides (e.g., apigenin 7-glucoside) and flavonols (e.g., quercetin glycosides and luteolin glucosides). The effect of drying on the total phenol content of aqueous chamomile extracts has been reported. Freshly extracted chamomile flowers had a higher content of phenols (19.7 ± 0.5 mg/g dry weight (dw)) compared to any of the dried samples, except for those that were freeze-dried ($p \leq 0.05$). There was no significant difference between the total phenol content in samples that were freeze-dried, air-dried, or oven-dried at 40ºC. However, a major decrease in the phenol concentration of chamomile flowers oven-dried at 80ºC (13 ± 1 mg/g dw; $p \leq 0.05$) was noted. Data showing the effect of drying on content of the flavonoid apigenin 7-glucoside were also presented. Extracts produced from fresh chamomile had an apigenin 7-glucoside content of 3.0 ± 0.4 mg/g dw, which was significantly higher than amounts reported for any of the dried samples ($p \leq 0.05$). There was no significant difference in the apigenin 7-glucoside content among the chamomile flowers that were freeze-dried, air-dried, or oven-dried at 40ºC (2.0 ± 0.4 mg/g dw). The greatest decrease in apigenin7-glucoside content (1.0 ± 0.3 mg/g dw) was observed in samples oven-dried at 80ºC.[15]

Chamomilla Recutita (Matricaria) Flower

Chamomilla recutita (matricaria) flowers contain a volatile oil (0.24 to 2.0%) that is blue in color.[16] The two key components (-)-alpha-bisabolol and chamazulene account for 50 to 65% of the total volatile oil content. Other components of the oil are as follows: (-)-alpha-bisabolol oxide A and B, (-)-alpha bisabolone oxide A, spiroethers (cis- and trans- en-yn-dicycloether, sesquiterpenes (anthecotulid), cadinene, farnesene, furfural, spathulenol, and proazulene (matricarin and matricine). Chamazulene is formed from matricine during steam distillation of the oil.

Chamomilla Recutita (Matricaria) Flower Oil

Chamomilla recutita (matricaria) flower oil contains anti-inflammatory and spasmolytic sesquiterpene lactones such as α-bisabolol, blue chamazulene (weaker anti-inflammatory effect), farnesene, polyenes, and several flavonoids.[17] *Chamomilla recutita* imported from Argentina may contain larger amounts of the strongly allergenic sesquiterpene lactone anthecotulide, and, additionally, may be contaminated with the morphologically similar dog fennel (*Anthemis cotula*), which contains up to 7.3% anthecotulide. However, *Chamomilla recutita* of European origin contains only traces of anthecotuliode. According to a more recent publication, anthecotulide was not detectable in 34 chamomile (*Matricaria recutita*) preparations.[18] These 34 chamomile preparations included preparations that were on sale in German public pharmacies, a number of herbal infusions from pharmacies and supermarkets, and some consumer products (e.g., shampoos) containing chamomile extracts.

The essential oil production of cultivated (BK-2, *Degumil*) and wild chamomile populations of 4 typical chamomile-rich regions of Hungary was studied.[19] The Hungarian BK-2 contained more chamazulene in its essential oil than the German *Degumil* type, which is cultivated mainly for α-bisabolol content. Both components have important anti-inflammatory activities. Wild populations can be easily distinguished from cultivated ones, based on their high content of bisaboloides. This is true particularly for the flower of Szabadkigyós wild type, for which the average content of biologically active (-)-α-bisabolol was 48%.

Chamomilla Recutita (Matricaria) Flower Oil
and Chamomilla Recutita (Matricaria) Flower Extract

Kamillosan® (an alcoholic extract of chamomile [*Chamomilla* (matricaria) *recutita*] flowers that contains 150 mg of chamomilla recutita (matricaria) flower oil), the hydroalcoholic extract (42% ethanol) of *Chamomilla recutita* (matricaria) flowers, and pure chamomilla recutita (matricaria) oil (plant part source not stated) were analyzed (using HPLC) to identify the coumarin derivatives umbelliferone and herniarin. Kamillosan® contained 41.8 µg umbelliferone/ml and 93.1 µg herniarin/ml, and the hydroalcoholic extract of *Chamomilla recutita* (matricaria) flowers contained 36.0 µg umbelliferone/ml and 114.0 µg herniarin/ml. Pure chamomilla recutita (matricaria) oil contained 540 µg herniarin/ml.[20] Information on Kamillosan® content is presented because it is tested in some of the studies included in this safety assessment. It should be noted that, according to the following statement, Kamillosan® may contain Roman chamomile (also known as *Chamaemelum nobile* or *Anthemis nobilis*) or German chamomile (also known as *Matricaria recutita* or *Chamomilla recutita*):[21] "In Europe, medicinal preparations are made containing either Roman chamomile (*Chamaemelum nobile*) or German chamomile (*Matricaria recutita*), both members of the Compositae (Asteraceae) family. On the continent, an ointment marketed under the name Kamillosan® contains German chamomile, while a product with the same name marketed in Britain contains Roman chamomile."

USE

Cosmetic

Chamomile (*Chamomilla recutita* (matricaria))-derived ingredients function mostly as fragrance ingredients and skin conditioning agents in cosmetic products.[1] Chamomilla recutita (matricaria) flower/leaf/stem extract, however, also functions as a flavoring agent and oral care agent.

Information on uses of these ingredients as a function of product type was supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2013.[22] The most frequently used ingredient (use in almost 1000 products) was chamomilla recutita (matricaria) flower extract. The Personal Care Products Council (Council) conducted a survey of ingredient use concentrations in 2013, indicating use at concentrations up to 0.5% (chamomilla recutita (matricaria) flower) in lipstick.[23]

As shown in Table 6, both VCRP uses and use concentration data were provided for the following 5 ingredients:

- chamomilla recutita (matricaria) extract
- chamomilla recutita (matricaria) flower
- chamomilla recutita (matricaria) flower extract
- chamomilla recutita (matricaria) flower/leaf extract
- chamomilla recutita (matricaria) flower oil

VCRP frequency of use data, but no use concentration data, were available for:

- chamomilla recutita (matricaria) flower water and
- chamomilla recutita (matricaria) oil

Use concentration data, but no VCRP data, were available for:

- chamomilla recutita (matricaria) flower powder

Neither VCRP data nor use concentration data were available for:

- chamomilla recutita (matricaria) flower/leaf/stem extract
- chamomilla recutita (matricaria) flower/leaf/stem water
- chamomilla recutita (matricaria) leaf extract

Cosmetic products containing chamomile-derived ingredients may be applied to the skin and hair, or, incidentally, may come in contact with the eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

The following ingredients are used in products that are sprayed (highest maximum use concentration = 0.01% chamomilla recutita (matricaria) flower extract in hairspray): chamomilla recutita (matricaria) extract, chamomilla recutita (matricaria) flower, chamomilla recutita (matricaria) flower extract, chamomilla recutita (matricaria) flower/leaf extract, and chamomilla recutita (matricaria) flower oil. Additionally, the following 2 ingredients are used in face powders (highest maximum use concentration = 0.002% chamomilla recutita (matricaria) flower/leaf extract]): chamomilla recutita (matricaria) extract and chamomilla recutita (matricaria) flower/leaf extract. Because these ingredients are used in aerosol/pump hair sprays (i.e., chamomilla recutita (matricaria) extract, chamomilla recutita (matricaria) flower, chamomilla recutita (matricaria) flower extract, chamomilla recutita (matricaria) flower/leaf extract, and chamomilla recutita (matricaria) flower oil) or powders (chamomilla recutita (matricaria) extract and chamomilla recutita (matricaria) flower/leaf extract), they could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm, compared with pump sprays.[24,25,26,27] 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.[24,25]

Non-Cosmetic

Chamomilla Recutita

The chamomile species used in medicine is *Chamomilla recutita*, and hydroalcoholic extracts of chamomile flowers are often used in ointments or creams (e.g., Kamilosan^{R}). Additionally, bath additives (e.g. Kamillobad^{R}) and mouth sprays (e.g., Kamillosan M Spray) containing chamomile extracts as the active ingredient are offered for topical and oral treatment.[11] The use of chamomile in aroma therapy for the treatment of patients with dementia has also been reported.[28] Regarding use in pharmaceurtical products, it should be noted that Matricaria (*Chamomilla recutita*) flowers, Matricaria oil (from flowers), and Matricaria liquid extract are listed in the British Pharmacopoeia.[29]

Chamomilla recutita (matricaria) (German chamomile) is listed among the spices and other natural seasonings and flavorings that are generally recognized as safe (GRAS) for their intended use in food for human consumption.[30] It is also listed among the spices and other natural seasonings and flavorings that are GRAS for their intended use in animal drugs, feeds, and related products.[31]

Chamomilla recutita (matricaria) flowers are listed among the essential oils, oleoresins (solvent-free), and natural extractives (including distillates) that are GRAS for their intended use in food for human consumption.[32] They are also listed among the essential oils, oleoresins (solvent-free), and natural extractives (including distillates) that are GRAS for their intended use in animal drugs, feeds, and related products.[33]

FDA has determined that the available data are inadequate for establishing general recognition of safety and effectiveness of chamomile (genus and species not stated) flowers as used in digestive aid drug products.[34]

The fragrant flowering heads of both German chamomile (*Chamomilla recutita*) and Roman chamomile (*Anthemis nobilis*) are collected and dried for use as teas and extracts.[35] Additionally, 2 ointments marketed under the name Kamillosan® are available in Europe, one containing German chamomile (also known as *Matricaria recutita* or *Chamomilla recutita*) and, the other, containing Roman chamomile (also known as *Chamaemelum nobile* or *Anthemis nobilis*).[21]

TOXICOKINETICS

In vivo data on the absorption, distribution, metabolism, and excretion of the *Chamomilla recutita*-derived cosmetic ingredients reviewed in this safety assessment were not found in the published literature, nor were unpublished data provided. However, because (-)-α-bisabolol, a constituent of chamomilla recutita (matricaria) flower oil, may be present at concentrations as high as 41.45%, the data presented in Table 1 relating to the absorption of and systemic exposure to bisabolol may be considered, including data addressing skin penetration, skin penetration enhancement, and repeated dose oral and dermal toxicity. In addition to these data, a summary of *in vitro* data on the transfer of volatile oil components is included below.

Using an *in vitro* membrane (cellophane membrane) diffusion model, chamomilla recutita (matricaria) oil was tested to identify components of the oil that are able to pass through membranes under different conditions.[36] The components of chamomilla recutita (matricaria) oil examined were: chamazulene, (-)-α-bisabolol, α-farnesene, β-farnesene, and matricin. In the diffusion model, the buffer solution (pH 1.1) used to represent the stomach was: 1 N HCl, NACl, and glycocol in water. The following buffer solution (pH = 7.5) was used to represent the plasma: Na_2HPO_3 and KH_2PO_4 in water. The transfer of chamomilla recutita (matricaria) oil from aqueous volatile oil to pH = 1.1 (stomach), and then from buffer pH = 1.1 to buffer pH = 7.5 (plasma) was studied. Transfer of the oil to the acidic moiety was faster than its transfer from buffer pH =1.1 to buffer pH = 7.5. Regarding transfer from aqueous solution to buffer pH = 1.1, 36.4% of the oil passed through the membrane; a value of 13.7% was reported in the case of transfer from buffer pH =1.1 to buffer pH = 7.5. With the exception of chamazulene, most of the components passed through the membranes.

TOXICOLOGY

Acute Toxicity

Oral

Chamomilla Recutita (Matricaria) Flower Extract

The acute oral toxicity of a lyophilized water extract of *Chamomilla recutita* (matricaria) flowers was evaluated using 2 groups of 12 female mice of the Swiss-NOS strain. Each group received a single oral dose of 720 or 440 mg/kg,, and was observed for 24 h post-dosing. None of the animals died, and there was no evidence of acute toxicity.

Chamomilla Recutita (Matricaria) Flower Oil

The acute oral toxicity of chamomilla recutita (matricaria) flower oil (dose = 5 g/kg) was evaluated using 10 rats (strain not stated).[37] Dosing was followed by a 14-day observation period. None of the animals died, and an LD_{50} of > 5 g/kg was reported. Consistent with these findings, acute oral LD_{50} values of 8,560 mg/kg and 10,000 mg/kg in rats have also been reported for chamomilla recutita (matricaria) flower oil, but details relating to the test protocol and study results were not included.[38]

Chamomilla Recutita (Matricaria) Flower Oil

In an acute toxicity study, doses of chamomilla recutita (matricaria) flower oil (10, 100, 1000, 1600, 2900, 4300, and 5600 mg/kg) were administered orally to groups of male NIH mice (number per group not stated).[39] The essential oil was obtained through a vapor distillation process, from the flowers of *Matricaria chamomilla*. The observation period was not stated. None of the animals died. This study was performed prior to the antigenotoxicity study summarized in the Genotoxicity section of this report.

Dermal

Chamomilla Recutita (Matricaria) Flower Oil

The acute dermal toxicity of chamomilla recutita (matricaria) flower oil (dose = 5 g/kg) was evaluated using 6 rabbits (strain not stated).[37] None of the animals died during the 14-day observation period, and an LD_{50} of > 5 g/kg was reported. The skin reactions observed are reported in the section on Skin Irritation.

Repeated Dose Toxicity

Animal

Chamomilla Recutita (Matricaria) Flower Extract

Prior to dosing, the blended flower powder of *Chamomilla recutita* (matricaria) was suspended in deionized water and kept in a water bath at 40˚C for 24 h. The mixture was filtered first with fine muslin cloth, and then with filter paper. The clear filtrate was dried in a water bath at 40˚C, and the clear paste obtained was used in the study. Sprague-Dawley rats of either sex (number not stated; males or females only not specified) received doses (1, 2, 4, and 8 g/kg body weight) of chamomilla recutita (matricaria) flower extract (aqueous extract), dissolved in water, for 14 days.[40] Additional details regarding the dosing procedure were not included. Neither signs of toxicity nor mortalities were observed at doses up to 4 g/kg body weight. Information relating to effects of the 8 g/kg dose was not included. All of the animals remained physically active.

Data on repeated dose toxicity were presented in a study on the effect of chamomile tea on the activity of hepatic phase I and phase II metabolizing enzymes from the rat.[41] Chamomile tea is made from the dried flower heads of *Chamomilla recutita* (matricaria). Five female Wistar rats (8 to 9 weeks old) had free access to Chamomile tea solution (2% w/v in water), whereas the control group had access to water. After 4 weeks of treatment, the animals were killed. Ingestion of the tea solution had no significant influence on body weight, and there were no signs of gross pathology of internal organs. Liver weight /body weight ratios of treated rats were not significantly different from control values.

Human

Chamomilla Recutita (Matricaria) Flower

Fourteen healthy volunteers (7 males, 7 females) were given 200 ml of chamomile tea (from *Chamomilla recutita* [matricaria] flowers) daily for 2 weeks. None of the subjects reported adverse effects after ingestion of the tea.[42] An analysis of urine samples collected before dosing, during the dosing period, and after dosing indicated that depletion of creatinine and the elevation of hippurate and glycine were strongly associated with chamomile tea intake.

Ocular Irritation

Chamomilla Recutita (Matricaria) Flower Oil

The hen's egg test – chorioallantoic membrane (HET-CAM assay) was used to determine the irritation potential of chamomilla recutita (matricaria) flower oil.[43] HET-CAM assays were performed with 6 replicates and repeated 3 times. The oil was applied to the CAM of fresh, fertile eggs that had been incubated for 72 h. Undiluted chamomilla recutita (matricaria) flower oil was not irritating to the hen's egg chorioallantoic membrane.

Chamomilla Recutita (Matricaria) Flower Extract

One of the trade name mixtures associated with chamomilla recutita (matricaria) flower extract has the INCI name, mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract (see Table 4). It is also known as vegetol matricaire 4140 huileux, contains 1 to 4.9% chamomilla recutita (matricaria) extract, and mineral oil and prunus armeniaca (apricot) kernel oil are the extraction solvents. The ocular irritation potential of this trade name mixture was evaluated using 6 male albino New Zealand white rabbits.[44] The mixture (0.1 ml) was instilled into the conjunctival sac of the right eye in each rabbit, and eyes were not rinsed. Reactions were scored at 1 h post-instillation and then at 1, 2, 4, and 7 days post-instillation. The trade name mixture was classified as a non-irritant in this study.

Another trade name mixture associated with chamomilla recutita (matricaria) flower extract has the INCI name, propylene glycol (and) water (and) chamomilla recutita (matricaria) flower extract (see Table 4 for composition). It is also known as vegetol matricaire mcf 793 hydro, contains 5 to 9.9% chamomilla recutita (matricaria) flower extract, and propylene glycol and water are the extraction solvents. The ocular irritation potential of this trade name mixture (diluted to 15% with sterile water; 0.1 ml instilled) was evaluated using 6 New Zealand rabbits.[45] Reactions were scored at 24 h, 48 h, and 72 h post-instillation. The trade name mixture (diluted to 15% and) was classified as a non-irritant.

The ocular irritation potential of a trade name mixture associated with chamomilla recutita (matricaria) flower extract (INCI name = propylene glycol (and) water, salvia officinalis (sage) leaf extract, and chamomilla recutita (matricaria) flower extract) was evaluated using 6 male albino New Zealand white rabbits.[46] The trade name mixture is also known as vegetol sp gr 051 hydro (extraction solvents = propylene glycol and water) and contains 0.1 to 0.9% chamomilla recutita (matricaria) flower extract. It was tested according to the protocol stated at the beginning of this section. Based on the results in this study, this trade name mixture was classified as a non-irritant.

Skin Irritation

Chamomilla Recutita (Matricaria) Flower Oil

In the acute dermal toxicity study on chamomilla recutita (matricaria) flower oil involving 6 rabbits (strain not stated), summarized earlier, the following skin reactions were observed after dosing (time period not stated) with 5 g/kg: slight redness (2 rabbits), moderate redness (4 rabbits), slight edema (2 rabbits), and moderate edema (4 rabbits).[37]

Undiluted chamomilla recutita (matricaria) flower oil was applied to the backs of hairless mice (number and strain not stated). Details relating to the test procedure were not included. The oil was classified as non-irritating.[7] In another experiment, chamomilla recutita (matricaria) flower oil was applied (under occlusion) to intact or abraded skin of rabbits (number and strain not stated) for 24 h. The oil was classified as moderately irritating.

Chamomilla Recutita (Matricaria) Flower Extract

One of the trade name mixtures associated with chamomilla recutita (matricaria) flower extract has the INCI name, mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract (see Table 4 for

composition). It is also known as vegetol matricaire 4140 huileux, contains 1 to 4.9% chamomilla recutita (matricaria) extract, and mineral oil and prunus armeniaca (apricot) kernel oil are the extraction solvents. The skin irritation potential of this trade name mixture was evaluated using 6 male albino New Zealand white rabbits.[44] A 14 cm x 14 cm area on the right flank was clipped free of hair and scarified. Skin of the left flank remained intact. The mixture was applied to the test sites (scarified and intact sites) at a rate of 0.5 ml^2 per area. The test site was then covered with a 2 cm x 2cm gauze pad, secured with another adhesive patch, for 23 h. Reactions were scored at 24 h and 72 h after patch application. The trade name mixture was classified as a non-irritant.

Another trade name mixture associated with chamomilla recutita (matricaria) flower extract has the INCI name, propylene glycol (and) water (and) chamomilla recutita (matricaria) flower extract (see Table 4 for composition). It is also known as vegetol matricaire mcf 793 hydro, contains 5 to 9.9% chamomilla recutita (matricaria) flower extract, and propylene glycol and water are the extraction solvents. The skin irritation potential of this trade name mixture (undiluted) was evaluated in the Draize test using 6 New Zealand rabbits, according to a procedure similar to that in the preceding study. The mixture was classified as a non-irritant.[45]

The skin irritation potential of a trade name mixture associated with chamomilla recutita (matricaria) flower extract (INCI name = propylene glycol (and) water, salvia officinalis (sage) leaf extract, and chamomilla recutita (matricaria) flower extract) was evaluated using 6 male albino New Zealand white rabbits.[46] The trade name mixture is also known as vegetol sp gr 051 hydro (extraction solvents = propylene glycol and water) and contains 0.1 to 0.9% chamomilla recutita (matricaria) flower extract. The test procedure is stated at the beginning of this section. The mixture was classified as a non-irritant.

Human

Predictive Testing

Chamomilla Recutita (Matricaria) Flower Oil

The skin irritation potential of chamomilla recutita (matricaria) flower oil (4% in petrolatum) was evaluated in a 48-h closed patch test involving human subjects (number not stated). Skin irritation was not observed.[7]

Predictive/Provocative Testing

Chamomilla Recutita (Matricaria) Flower Extract

The skin irritation potential of a cuticle softener containing 0.3% chamomilla recutita (matricaria) flower extract was evaluated in an epicutaneous patch test using 50 subjects (19 to 63 years old; sex distribution non-standardized) who were classified as follows: 29 normal, healthy subjects, 3 with eczema, 1 with an allergy, and 17 with sensitive skin.[47] Chamomilla recutita (matricaria) flower extract was prepared by supercritical fluid extraction with carbon dioxide, and consists of the following components: 8-15% essential oil with 10-25% bisabolol and 5-35% bisabolol oxides, 0.8-2.5% matricine (analyzed as chamazulene), cis- and trans-en-in dicycloether, spartulenol, herniarine, waxes, and non-volatile components. The undiluted product was applied to the back (test area dimensions not stated) for 48 h using Haye's Test chambers (square test chambers). Sodium dodecyl sulfate (1% in water) and water served as positive and negative controls, respectively. Reactions were scored 30 minutes after patch removal and at 72 h post-application. The product did not induce skin irritation in any of the subjects tested. The positive control caused skin irritation in 15 subjects, and there were no reactions to the negative control. The product was classified as harmless relative to its skin irritation potential.

Skin Irritation and Sensitization

Animal

Chamomilla Recutita (Matricaria) Extract

The cross reactivity of carabron (sesquiterpene lactone isolated from *Arnica longifolia*) with chamomilla recutita (matricaria) extract was evaluated using 5 female albino guinea pigs of the Pirbright white strain.[48] The chamomilla recutita (matricaria) extract tested was a *Chamomilla recutita* (Matricaria) whole plant ether extract. A 10% acetone solution of carabron (0.05 ml) was applied daily (weekends excluded) to a 2 cm^2 area of the clipped and shaved flanks; slight erythema developed on day 9. Neither the application of patches nor the test substance application period was mentioned in this study. Applications were continued for up to a period of 4 weeks and were discontinued when a strong inflammatory reaction (+++) was observed. The challenge phase was initiated 2 weeks after the end of the induction phase. Four different concentrations

of carabron (0.3%, 1%, 3%, and 10%) were applied to the opposite flank. Challenge reactions (slight spotty erythema, down to the 0.3% dilution) were observed in all animals. The animals were also challenged with 10% chamomilla recutita (matricaria) extract, and there were no sensitization reactions in any of the 5 guinea pigs previously sensitized to carabron.

Human

Predictive Testing

Chamomilla Recutita (Matricaria) Flower Extract

A human repeated insult patch test on a shave balm containing 0.2% chamomilla recutita (matricaria) flower extract was performed using 105 subjects (males and females; mean age = 47).[49] Initially, each subject received nine 24 h induction applications of the test substance (0.2 ml; test area dimensions not stated), using occlusive patches. The induction phase was followed by a 10- to 15-day non-treatment period. A 24 h occlusive patch containing the test substance (0.2 ml) was applied to each subject during the challenge phase. Adverse events were not reported during the study, and the authors concluded that there was no evidence that the product induced skin sensitization.

The skin sensitization potential of an eye lotion containing 0.4% chamomilla recutita (matricaria) flower extract was evaluated in an HRIPT using 107 healthy subjects (males and females; between 18 and 70 years old).[50] A semiocclusive patch containing the test substance (volume and application area not stated) was applied to the upper back, between the scapulae, for 24 h on Mondays, Wednesdays, and Fridays. This procedure was repeated for a total of 9 induction applications (same test site). Reactions were scored 24 h after patch removal on Tuesdays and Thursdays, and 48 h after patch removal on Saturdays. Following a 2-week, non-treatment period, a challenge patch was applied for 24 h to a previously untreated site on the back. Reactions were scored at the time of patch removal and at 48 h and 72 h. Dermal reactions were not observed at any time during the study. The authors concluded that the eye lotion did not exhibit a clinically significant potential for eliciting dermal irritation or sensitization.

Chamomilla Recutita (Matricaria) Extract

The skin irritation and sensitization potential of facial cleansing and makeup remover towelettes containing 0.01% chamomilla recutita (matricaria) extract was evaluated in an HRIPT involving 50 subjects (ages not stated).[51] The product was tested, under occlusive conditions, as a mixture of the wipe fabric and the material with which the wipe was impregnated. Patches were applied to the back (same site, area dimensions not stated) for a total of 9, 24 h induction applications. Following a 2-week non-treatment period, challenge patches were applied for 24 h to the same sites used for induction. Reactions were scored at 24 h, 48 h, and 72 h post-application. The product did not cause skin irritation or allergic contact dermatitis in any of the subjects tested.

Chamomilla Recutita (Matricaria) Flower/Leaf Extract

A hair gel styling mist containing 0.00006% chamomilla recutita (matricaria) flower/leaf extract was evaluated for skin irritation and sensitization potential using 103 subjects (ages not stated).[52] The HRIPT procedure was the same as in the preceding study, except that semiocclusive patches were used and challenge sites were scored at 24 h and 72 h post-application. The volume applied and dimensions of the test aerea were not stated. The product did not cause skin irritation or allergic contact dermatitis in any of the subjects tested.

Chamomilla Recutita (Matricaria) Flower Oil

The skin sensitization potential of chamomilla recutita (matricaria) flower oil was evaluated in the maximization test using 25 healthy volunteers (21 to 42 years old).[53] The test material (4% in petrolatum) was applied, under occlusion, to the volar forearm of each subject for a total of 5 alternate-day 48-h periods. The test site was pre-treated with 5% sodium lauryl sulfate (24-h application, under occlusion) prior to application of the test material. A 10-day non-treatment period was observed after the induction phase. Challenge patches were then applied, under occlusion, to new test sites for 48 h. The application of challenge patches was preceded by a 1-h application of 10% aqueous sodium lauryl sulfate (under occlusion). Reactions were scored at the time of challenge patch removal and 24 h later. There was no evidence of contact sensitization in any of the subjects tested.

Provocative Testing

Chamomilla Recutita (Matricaria)
Chamomilla Recutita (Matricaria) Extract

The skin sensitization potential of chamomilla recutita (matricaria) extract (ether extract) was studied using 24 patients (men and women; age range: 23 to 82 years) with Compositae allergy.[54] The plant extract (1%) was applied to the back of each patient using Finn chambers on Scanpor®. Patch test reactions were scored at 2, 3, or 4 days, and, frequently, on days 5 to 7, according to the International Contact Dermatitis Research Group (ICDRG) grading scale. An additional group of 5 patients was also patch tested with the plant extract (2.5% in petrolatum). Of the 24 patients, 18 (i.e. 75%) had positive reactions to 1% chamomilla recutita (matricaria) ether extract. Most of the reactions were ++ (9 patients) and 2 patients had a +++ reaction. Additionally, 7 patients had a + reaction and 3 patients had a doubtful (?+) reaction. Of the 5 patients, 4 had positive reactions (scores not stated) to 2.5% chamomilla recutita (matricaria) ether extract. The 5 patients were also involved in a standard photopatch test, and the results are included in the section on Phototoxicity.

The frequency of allergic reactions to a Compositae plant mixture containing chamomilla recutita (matricaria) extract (ether extract) was evaluated using 3,851 patients (ages not stated) patch tested between 1985 and 1990.[55] Other components of the plant mixture included: Ether extracts of arnica, feverfew, tansy, and yarrow. Eighty-four patients (ages not stated) were patch-tested with chamomilla recutita extract (ether extract; test concentration = 2.5%) during the same period. The ether extract was prepared by cutting the fresh plant material (all above-ground parts) into 20 cm long pieces and extracting them with diethyl ether. Patches (Finn chambers on Scanpor) were secured to the back of each subject, using self-adhesive tape, for 24 h. Reactions were scored according to International Contact Dermatitis Research Group (ICDRG) recommendations. Positive reactions (at least ++) to the Compositae plant mixture were observed in 118 patients (3.1% of 3,851 patients tested). Of the 85 patients tested, there were 48 (56.5% of patients tested) positive reactions to chamomilla recutita extract.

Another study to investigate the frequency of *Compositae* (*Asteraceae*, daisy family) sensitivity was performed.[56] Thirty adult patients (24 females, 6 males; mean age = 34.7 years) with "extrinsic" atopic dermatitis were patch tested with *Chamomilla recutita* (matricaria, 2.5% in petrolatum), sesquiterpene lactone mix (SL mix, 01% in petrolatum), and *Compositae* mix (C mix, 6% in petrolatum). The C mix contained the following ingredients: arnica (*Arnica Montana*) extract, chamomile (*Chamomilla recutita*) extract, tansy (*Tanacetum vulgare*) extract, feverfew (*Tanacetum parthenium*) extract, and yarrow (*Achillea millefolium*) extract. Patch testing was performed using Finn chambers on Scanpor® and Curatest®. Reactions were scored on days 2 and 3, and, where possible, on days 5 through 8 according to a grading scale (- to +++) recommended by the International Contact Dermatitis Research Group (ICDRG). A total of 9 patients reacted to SL mix and/or C mix. Of these 9, 5 had positive reactions to *Chamomilla recutita* (matricaria). All of the patients sensitive to *Chamomilla recutita* (matricaria) were C mix positive.

Danish gardeners and greenhouse workers (19, ages not stated) with Compositae-related symptoms were patch tested with 2.5% *Chamomilla recutita* (matricaria) in petrolatum.[57] The test protocol was not included in this study. Positive reactions were observed in 11 of the 19 patients tested (58% sensitization rate).

From 1991 to 2009, selected patients with known or suspected Compositae allergy were patch tested. Of the 36 patients (ages not stated) patch tested with ether extracts of *Chamomilla recutita* (matricaria), 30 (or 94%) had positive patch test reactions.[58] The majority of these reactions (90%) were strongly positive (++ or +++ reactions); the relevance was most frequently recorded as unknown.

Chamomilla Recutita (Matricaria) Extract and Tea

A conjunctival provocation test was performed on 7 hay fever patients who had experienced conjunctivitis after ocular rinsing with *Chamomilla recutita* (matricaria) tea (from flower heads).[59] *Chamomilla recutita* (matricaria) tea extract (tea extracted in phosphate-buffered saline) was evaluated in the provocation test. Initially, one drop of the tea extract (1:1,000,000 wt/vol) was instilled into the conjunctival sac. If a reaction was not observed within 20 minutes, the next concentrations (progressively increased by ten-fold) were instilled into the conjunctival sac of the other eye. The conjunctivitis initially experienced after ocular rinsing with the tea was reproduced via conjunctival provocation. Two of the patients had a positive conjunctival response to very dilute solutions of the extract (1:100,000 wt/vol and 1:1,000,000 wt/vol, respectively). Three and two patients had positive responses to 1:1000 w/v and 1:100 w/v, respectively. Additionally, all 7 patients had positive skin prick tests to the tea extract. Only 2 of the 100 control hay fever patients had a positive conjunctival reaction to the tea extract, suggesting to the authors that these were not irritant reactions. It was concluded that ocular rinsing with *Chamomilla recutita* (matricaria) tea can induce allergic conjunctivitis.

The allergenicity of chamomilla recutita (matricaria) extract was evaluated using 9 patients (7 women, 2 men; mean age = 36 years).[60] These patients had a history of systemic allergic reactions after ingestion of honey and/or after drinking *Chamomilla recutita* (matricaria) tea (from flower heads). To produce the plant extract, *Matricaria chamomilla* was defatted with acetone and macerated in phosphate buffered saline. The mixture was then stirred, centrifuged, and filtered. The extract (3.5 mg/ml) was applied to the volar surface of the forearm and a prick test was performed. Skin sites were examined after 15 minutes, and a positive reaction was defined as a wheal with a diameter > 3 mm. Twenty subjects (10 atopic, 10 nonatopic) served as controls. A positive reaction to chamomilla recutita (matricaria) extract was observed in all 9 patients. Results were negative in the 20 control subjects. A CAP inhibition assay (i.e., inhibition of binding of specific IgE to Andujar honey) was also performed. Precipitation of food allergy reactions is well known in some patients with pollinosis when they consume natural food, such as honey or chamomile tea. The Pharmacia CAP system (fluorometric assay) used is a system for titration of total and specific IgE. Pooled serum was obtained by mixing equal parts of serum from 5 of the 9 patients with the soluble extract of *Chamomilla recutita* (matricaria) pollen (358 µg protein/ml). Duplicate 100-µl aliquots of serial two-fold dilutions (in phosphate buffered saline [PBS]) of the competing fluid-phase antigen were incubated (2-h incubation period) with an equal volume of serum from the serum pool. Fluorometric assay was performed at the end of the incubation period. Percent inhibition for each dilution was calculated, and the concentration of the extract that caused 50% inhibition of IgE binding to Andujar honey (C_{50}) was determined. A C_{50} of 45.72 µg/ml was reported for chamomilla recutita (matricaria) extract.

In the same study, the 9 patients were subjected to a conjunctival challenge with *Chamomilla recutita* (matricaria) tea (from flower heads). One drop of phosphate buffered saline (PBS, negative control) was placed in the conjunctival sac. If a reaction was not observed, the tea (1 drop per dilution, every 15 minutes) was instilled as a series of 10-fold dilutions in PBS. The initial dilution instilled was $1:10^5$ (w/v). A positive reaction was defined by congestion of the conjunctival mucosa and itching of the eye. The same 20 subjects (10 atopic, 10 nonatopic) served as controls. A positive reaction to *Chamomilla recutita* (matricaria) tea was observed in all 9 patients, only at low-level dilutions (1/10 or 1/100). Results were negative in the 20 control subjects.[60]

Chamomilla Recutita (Matricaria) Extract

The skin sensitization potential of chamomilla recutita (matricaria) extract was evaluated using 76 patients, all sensitive to 6% *Compositae* mix (contains chamomilla recutita (matricaria) extract) in petrolatum.[61] The extraction solvent for each extract was not stated. Chamomilla recutita (matricaria) extract (2.5% in petrolatum) was applied to the back for 2 days using Finn chambers on Scanpor® tape. Reactions were scored on days 3 to 5, and possibly, on day 7 according to ICDRG criteria. Of the 76 patients, 49 had positive reactions to the extract. In a subsequent test (same procedure), 52 of the 76 patients had positive reactions to the extract.

Chamomilla Recutita (Matricaria)
Chamomilla Recutita (Matricaria) Flower Extract

A skin sensitization study was performed using 35 patients (26 women, 9 men; mean age = 59) sensitive to sesquiterpene lactones mix and 22 control patients (17 women, 5 men; mean age = 52) who were not sensitive to sesquiterpene lactones mix.[62] All patients were patch tested with the following: chamomilla recutita (matricaria) flower extract (1, 3, 10, 32, and 100% aqueous extract) and chamomilla recutita (matricaria) (2.5% w/w in petrolatum). Chamomilla recutita (matricaria) flower extract was actually an aqueous extract of *Chamomilla recutita* tea (from dried flower heads). Each test substance concentration (15 µl) was applied to the back using a Finn chamber (8 mm diameter) on Scanpor® tape. Chambers were removed after 2 days. Reactions were scored according to ICDRG recommendations on days 3 and 7. The numbers of patients with positive reactions to chamomilla recutita (matricaria) flower extract were as follows: 100% aqueous (30 patients; + to +++ reactions), 32% aqueous (27 patients; + to +++ reactions), 10% aqueous (21 patients; + to +++ reactions), 3% aqueous (14 patients; + to +++ reactions), and 1% aqueous (9 patients; + to +++ reactions). The number of patients with +++ reactions decreased with decreasing aqueous flower extract concentration. Of the 35 patients patch tested with *Chamomilla recutita* (matricaria) (2.5% w/w in petrolatum), 22 had positive reactions (+ to +++). The following 2 of 22 control patients (not sensitive to sesquiterpene lactones mix) had positive reactions to chamomilla recutita (matricaria) flower extract: subject 1 (++ reaction to 100% aqueous and subject 2 (++ [100% aqueous], + [32% aqueous], ++ [10% aqueous], + [3% aqueous], and + [1% aqueous].

Chamomilla Recutita (Matricaria) Flower Extract

The sensitization potential of wild chamomilla recutita (matricaria) flower extract (extraction solvent not stated) in 129 patients sensitive to Compositae mix was evaluated.[63] Patches (Finn chambers on Scanpor) containing 2.5% chamomilla recutita (matricaria) flower extract in petrolatum remained in place for 2 days. Reactions were scored on days 2 to 4, and,

whenever possible, on days 5 to 8 according to ICDRG recommendations. Of the 129 patients, 83 (64%) had positive reactions to the test material. When 74 chrysanthemum-positive patients were patch-tested with wild chamomilla recutita (matricaria) flower extract (2.5% in petrolatum), 58 (78%) had positive reactions.

The skin sensitization potential of aqueous extracts of *Chamomilla recutita* (matricaria) tea (from flower heads) was evaluated using 20 patients (13 women, 7 men; mean age = 56 years) with known contact allergy to sesquiterpene lactone mix (containing altolactone, costunolide, and dehydrocostuslactone).[64] Aqueous extracts (1%, 10%, and 100%) of 2 different kinds of *Chamomilla recutita* (matricaria) tea (identified as I and II) were tested. Each solution (15 µl) was applied to the back, using a Finn chamber on Scanpor tape, for 48 h. Reactions were scored on days 3 and 7 according to ICDRG recommendations. For 9 of the 20 patients, reactions were also scored on day 10. The following positive reactions to *Chamomilla recutita* (matricaria) tea I were reported: 1% aqueous (2 reactions, + and ++), 10% aqueous (4 reactions, + to ++), and100% aqueous (11 reactions, ++ predominated). The following positive reactions to *Chamomilla recutita* (matricaria) tea II were reported: 1% aqueous (1 reaction, ++), 10% aqueous (10 reactions, + to +++; mostly ++), and 100% aqueous (11 reactions, + to +++; mostly ++).

Chamomilla Recutita (Matricaria) Extract
Chamomilla Recutita (Matricaria) Flower Oil

Up to 14 adult patients who had previously tested positive (at least a 2+ reaction) to ether extracts of *Chamomilla recutita* (2.5% in petrolatum) and/or *Arnica montana* (0.5% in petrolatum) were patch tested with the following: *Chamomilla recutita* (2.5% in petrolatum) and chamomilla recutita flower oil (1% and 4% in petrolatum).[65] A patch (Finn chambers on Scanpor® tape) containing either of the test materials was applied to the back for 2 days. Reactions were scored on day 3, and, possibly, day 7 according to ICDRG recommendations. Of the 10 patients patch tested with *Chamomilla recutita* (2.5% in petrolatum), 9 had positive reactions (+ to +++) and 1 had a doubtful positive follicular reaction. Only 2 of 14 patients had reactions to chamomilla recutita flower oil (doubtful positive reaction to 4 % [1 patient]; ++ reaction to 4% and 1% [1 patient]).

Chamomilla Recutita (Matricaria) Flower Oil

The skin sensitization potential of chamomilla recutita (matricaria) flower oil (2% in yellow, soft paraffin) was evaluated using 74 patients (ages not stated), all negative to balsam of Peru.[66] Of the 74 patients, 3 were positive to chamomilla recutita (matricaria) flower oil. Though negative to balsam of Peru, these 3 patients were also positive to 1 or more of the 3 other balsams (colophony, turpentine, and wood tars: *oleum betule* and *oleum fagi*). Details relating to the test procedure were not stated.

Of 200 patients patch tested with chamomilla recutita (matricaria) flower oil in Poland, 2 positive reactions were reported.[67] Details relating to the patch test procedure were not included.

Eighty-six patients with positive reactions to a perfume mixture containing the following ingredients were tested with chamomilla recutita (matricaria) flower oil:[68] eugenol, isoeugenol, cinnamic aldehyde, geraniol, cinnamic alcohol, oakmoss absolute, hydroxycitronellal, and amyl cinnamic alcohol. Neither the test concentration of chamomilla recutita (matricaria) flower oil nor details relating to the test protocol were included. Two (or 3.4%) of the 86 patients were sensitive to the oil.

Case Reports

Chamomile/Chamomile Extract

Rapid onset of a transient rash, burning, stinging, and itching at the application sites were reported for a 24-year-old woman who had applied a cosmetic skin mask formulation to her face.[69] Components of the skin mask were as follows: whole egg, lecithin, allantoin, aloe gel, melissa extract, and chamomile extract (extraction solvent not stated). The genus and species of the chamomile extract were not stated. Open testing (i.e., without prick, scratch, or chamber) with 1% chamomile extract (in physiologic saline) produced an extensive wheal and flare reaction on intact forearm skin. Open test results were negative for the saline control and 1% chamomile extract in 10 control subjects. The authors concluded that the patient appeared to have developed immunologic contact urticaria.

A 20-year-old woman complained of a short-lasting cough and rhinitis after inhaling fragrance from a chamomile-scented toilet paper.[70] The genus and species of the chamomile were not stated. Chamomile allergenicity was evaluated in a

prick test and radioallergosorbent test (RAST). Results for the prick test (wheal mean diameter = 12 mm) and RAST (Pharmacia ImmunoCAP system (CAP system): 12.9 KU/l (v.n. < 0.35) were positive. Results were also positive when the chamomile-scented toilet paper was evaluated in a prick-by-prick test (mean diameter of wheal = 9 mm (toilet paper) and 5 mm (histamine). Two atopic subjects and 2 healthy subjects served as controls for the prick-by-prick test, and results were negative for the chamomile-scented tissue.

Chamomilla Recutita (Matricaria) Flower

Occupational dermatitis of the hands was observed in a 27-year old florist, and patch test results revealed positive reactions to the petals and leaves of *Matricaria recutita* (*also Chamomilla recutita*).[71] Details relating to the patch test procedure were not included.

Delayed-type contact dermatitis of the face was observed in a 62-year-old female who worked in a flower stall 1 day per week.[72] The patient presented with a relapsing dermatitis of the face for 1 year. Relapse of dermatitis was observed within 24 h of working a single afternoon in the shop. Patch test results indicated positive reactions to the flowers, petals, and stems of *Matricaria recutita*. Details relating to the patch test procedure were not included.

A 54-year-old female cosmetician complained of sneezing, coughing (with occasional dyspnea), orbital pruritus, dacryorrhea, and rhinitis.[73] Her work involved the preparation and application of herbal beauty masks containing 24% chamomile flower (*Matricaria chamomilla*). Dermatitis of both hands, with intermittent vesiculation, was observed. Open patch testing (immediate reactions read after 30 and 60 minutes) revealed a positive reaction to chamomile flower. The diameter of the wheal was ≈1 cm. A positive prick test reaction (++) to chamomile pollen was also reported. A provocation test was performed using acoustic rhinometry, and the duration of exposure to chamomile flower was 3 minutes. Sneezing, dyspnea, and nasal chonchae swelling and hyperemia were reported. The decrease in volume of the nasal cavities was 3x that of the normal volume. Results of the provocation test were classified as strongly positive.

A 22-year-old female with facial eczema had been a frequent drinker of steaming-hot chamomile tea over the past year.[74] At times, the facial eczema was accompanied by lip swelling. Patch testing revealed a + D2/++ D4 reaction to 2.5% *Chamomilla recutita* in petrolatum. During follow-up at 4 months, the patient reported that she no longer drank chamomile tea and that there had been no further relapses of the eczema. It should be noted that the fragrant flowering heads of both German chamomile (*Chamomilla recutita*) and Roman chamomile (*Anthemis nobilis*) are collected and dried for use as teas and extracts.[35]

A 41-year-old atopic woman with hand eczema reported that she had not used chamomile tea externally, but had used the tea when treating her dog's inflamed eyes.[58] When patch tested, a +? follicular reaction to *Chamomilla recutita* (2.5% in petrolatum) was reported. In a subsequent identical patch test one month later, a ++ reaction was reported.

Chamomilla Recutita (Matricaria) Flower Extract

An 8-year old boy with hay fever and bronchial asthma had a severe anaphylactic reaction after ingestion of a *Matricaria chamomilla*-tea (from flower heads) infusion for the first time.[75] At 2 weeks after the reaction occurred, the patient was subjected to a skin prick test, beginning with a 1:100,000 wt/vol concentration of *Matricaria chamomilla* tea extract (tea extracted in phosphate-buffered saline). Skin test sites were read after 15 minutes, and a wheal of at least 3 mm x 3 mm was considered a positive reaction. Ten patients with hay fever and 10 normal subjects served as controls. Testing at a concentration of 1:100 wt/vol elicited a 4 mm by 6 mm wheal. None of the control subjects reacted to the tea extract. The enzyme-linked immunosorbent assay (ELISA) was used to test the 8-year-old patient's serum for specific IgE antibodies to antigens contained in the tea extract. IgE activity toward the tea extract was noted; however, this was not true for serum samples from 22 healthy subjects or from 5 patients with hay fever.

Acute eczema on the forearms and hands was observed in a 50-year old metalworker after using a product for cleaning metallic items.[76] The patient had no personal or family history of atopy, but had psoriasis. Treatment of the eczema involved washing and applying compresses (over 2-month period) with *Chamomilla recutita* (matricaria) tea (from flower heads). Patch tests were performed using Finn chambers; neither the area of application nor test concentration was stated. The following reactions were reported: Treatment with *Chamomilla recutita* (matricaria) tea resulted in a + reaction on day 2 and a ++ reaction on day 4. Negative results were reported for 5 control subjects tested with the tea.

A healthy, 35-year-old pregnant woman was given an enema containing glycerol and Kamillosan® (oily extract of *Chamomilla recutita* (matricaria) flowers).[77] The extraction solvent was not stated. Urticaria, larynx edema, tachycardia, and

hypotension followed, indicative of an anaphylactic reaction. In the skin prick test, Kamillosan® induced a 5 x 5 mm wheal reaction.

Eyelid angioedema was observed in a 23-year-old female after applying compresses of chamomile tea (obtained from the dried flower heads of *Chamomilla recutita*).[78] She had a history of seasonal rhinitis, conjunctivitis, and exercise-induced asthma. Prick test results were positive (++) for chamomilla recutita (matricaria) flower extract (extraction solvent not stated), and the level of IgE antibody was expressed as 3.37 kUA/l. In a subsequent oral challenge test performed with diluted chamomile tea, generalized pruritus of the face was the only symptom observed. The patient was diagnosed as having immune-mediated contact urticaria.

Work-related rhinoconjunctivitis and asthma were diagnosed in a 43-year-old man 11 years after he began working at a tea-packing plant.[79] The plant processed black tea (*Camellia sinensis*) as well as various herbal teas, including tea from chamomile flowers (*Chamomilla recutita*), lime (*Tilia cordata*), and dog rose. His symptoms occurred when chamomile tea was packaged. Furthermore, he became symptom-free when the production of herbal teas was transferred to another factory. A skin prick test with chamomile extract at a concentration of 10 mg/ml elicited a 6-mm wheal response. Prick test results were negative for black tea and lime tea extracts.

Phototoxicity

Chamomilla Recutita (Matricaria) Extract

Five patients were initially patch tested (Finn chambers on Scanpor® tape) with 2.5% chamomilla recutita (matricaria) ether extract, and the results were positive in 4 patients. The 5 patients were also evaluated in a standard photopatch test. The first reading (day 1) was followed by UV-irradiation and a second reading at day 3. Additional details regarding the test procedure were not included. Photoaggravation (score not provided) was observed in one of the 5 patients.[54]

Chamomilla Recutita (Matricaria) Flower Oil

Chamomilla (matricaria) flower oil (non-viscous, tested as received) was evaluated for phototoxicity using 12 Skh:hairless-1mice and 2 miniature swine.[80] The light source was a 6-kW long-arc xenon high pressure burner (UVA and UVB proportions approximated those found in mid-latitude summer sun spectrum) or a bank of 4 fluorescent F40BL black light lamps (UVA region, centered over 350 nm). A single application of the oil (20 µl) was made to an area of the back that was approximately 2 cm^2. Six mice and 1 swine were then exposed to one of the light sources, and, the remaining 6 mice and 1 swine, to the other light source at 30 minutes post-application of the oil. The duration of exposure to the fluorescent blacklight source was 1 h (integrated UVA intensity = 3 W/m^2), and, 40 minutes (intensity of weighted erythemal energy = 0.1667 W/m^2), to the xenon lamp. If application of the oil elicited a response from skin exposure to the blacklight lamp or elicited more than a barely perceptible response to the xenon lamp, the oil was considered phototoxic. The area of skin treated with the oil, but not irradiated, served as the control for primary irritant reactions. One group of control mice was treated with 8-methoxypsoralen (8-MOP, 0.01% in methanol), and another group was treated with an appropriate vehicle only. Exposure to the xenon lamp caused barely perceptible erythema in animals pretreated with vehicle only or with chamomilla (matricaria) flower oil. Parallel results were obtained using the blacklight lamp. 8-MOP was phototoxic.

Suppression of Sensory Irritation

Chamomilla Recutita (Matricaria) Flower Oil

Chamomilla recutita (matricaria) flower oil (German chamomile oil, bisabololoxide A type) was evaluated for its effect on capsaicin-induced sensory irritation in mice.[81] The intradermal injection of capsaicin into the mouse paw resulted in dose-dependent, paw-licking behavior due to sensory irritation. Co-administration of the oil suppressed this behavior in a dose dependent-manner over the 1% to 5% concentration range. The source of this information is an abstract of a Japanese study.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Chamomile

An epidemiology study examined the use of herbal products by pregnant women in Italy and pregnancy outcome.[82] The number of subjects (mostly between 31 and 40 years old) interviewed was 392. Of the 392 subjects, 109 reported having taken one or more herbal products during pregnancy; the remaining 283 were classified as non-users. The most frequently used herb was chamomile (48; 44% of the 109 subjects), followed by licorice (15; 13.8% of the 109 subjects). For the 37 regular users of chamomile and 14 regular users of licorice, there was a higher frequency of threatening miscarriages (21.6% and 35.7%, respectively) and preterm labors (21.6% and 16.7%, respectively) when compared to non-users. Whether or not the frequency of threatening miscarriages in users of chamomile versus non-users was statistically significant was not stated. An unspecified cardiac malformation (thought to have been related to Down's syndrome) and an enlarged kidney were diagnosed in 2 neonates, following regular maternal consumption of chamomile. Regarding pregnancy outcome in the study population, no statistically significant differences were evident between users and non-users, except for a higher incidence of newborns small for gestational age (11.9% vs. 5.3%; $p = 0.039$). However, after further analysis of the data, it was noted that a possible influence of regular intake of 2 herbs (chamomile and licorice, taken from the beginning of pregnancy) on threatening miscarriages and preterm labors of low birth weight infants could be hypothesized.

GENOTOXICITY

Chamomilla Recutita (Matricaria) Flower Oil

The genotoxicity of chamomile recutita (matricaria) flower oil was evaluated using 5 groups of five male NIH mice. Three groups of mice received oral doses of 10, 100, and 1000 mg/kg, respectively.[39] The extract of the essential oil (extraction solvent not stated) was obtained through a vapor distillation process, from the flowers of *Matricaria chamomilla*. The negative control group was dosed orally with corn oil and the positive control group was dosed intraperitoneally (i.p.) with an aqueous solution of methyl methanesulfonate (25 mg/kg). Following injection with an aqueous suspension of 5-bromodeoxyuridine (BrdU) and then colchicine, the mice were killed and bone marrow cell suspensions prepared for microscopic examination. At each dose, the incidence of sister chromatid exchanges was comparable to that noted in bone marrow cells from control animals (i.e., not more than 1.1). A high incidence of SCE's was observed after dosing with MMS, and the difference between this incidence and that for animals dosed with corn oil was statistically significant ($p < 0.05$). Additionally, when compared to control values, chamomile recutita (matricaria) flower oil produced a non-significant cytotoxic effect. The results for an acute oral toxicity preliminary test on the crude oil are included in that section of this report.

Chamomilla Recutita (Matricaria) Flower Extract

One of the trade name mixtures associated with chamomilla recutita (matricaria) flower extract has the INCI name, mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract (see Table 4 for composition). It is also known as vegetol matricaire 4140 huileux, contains 1 to 4.9% chamomilla recutita (matricaria) flower extract, and mineral oil and prunus armeniaca (apricot) kernel oil are the extraction solvents. The genotoxicity of this mixture (in DMSO) was evaluated in the Ames test using the following bacterial strains with and without metabolic activation: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2 *uvrA* pKM101.[83] The mixture was tested at doses up to 5,000 µg/plate. DMSO served as the negative (vehicle) control, and the following positive controls were used: 2-nitrofluorene, sodium azide, 9-aminoacridine, methyl methanesulfonate, and 2-aminoanthracene. Neither signs of toxicity or a precipate were observed over the range of doses tested. When compared to the negative control, the statistically significant increases in the number of revertants observed in strain TA100 without activation or in strain WP2 *uvrA* pKM101 with activation were slight, but there was no dose-relationship associated with these findings. Therefore, these changes were considered biologically insignificant. The authors concluded that the trade name mixture did not induce any biologically relevant increase in the number or revertants in any of the strains, with or without metabolic activation.

Antigenotoxicity

Chamomilla Recutita (Matricaria) Flower Oil

Chamomile recutita (flower) oil-induced inhibition of genotoxicity produced by daunorubicin (DAU, mutagen) and the genotoxicity of the oil were evaluated using the following groups of 5 male NIH mice:[84] control group administered corn oil orally (0.1 ml), positive control group treated with corn oil (0.1 ml) and DAU administered by intramuscular injection (10 mg/kg), a group administered chamomile recutita (flower) oil (500 mg/kg), and 3 groups treated with DAU and chamomile recutita (flower) oil (5, 50, and 500 mg/kg), respectively. Specifically, the effect of the 3 doses of essential oil on the rate of sister chromatid exchange (SCE) induced by DAU in spermatogonia was studied. Chamomile recutita (flower) oil was not genotoxic. However, dosing with this essential oil resulted in inhibition of SCE induced by DAU, and % inhibition was as follows at administered doses of the oil: 5 mg/kg (47.5% inhibition), 50 mg/kg (61.9% inhibition), and 500 mg/kg (93.5% inhibition).

Chamomilla Recutita (Matricaria) Flower Oil

Antigenotoxicity studies were performed using groups of 5 male NIH mice. The extract of the essential oil (extraction solvent not stated) obtained through a vapor distillation process from the flowers of *Matricaria chamomilla* was evaluated. When compared to mice dosed with corn oil**,** sister chromatid exchanges induced by daunorubicin were decreased in mice pre-treated with crude chamomile recutita (matricaria) flower oil at doses ranging from 5 to 500 mg/kg.[39] Administration of the crude oil to daunorubicin-treated mice caused a statistically significant, dose-dependent reduction in the genotoxic damage (SCE's). The antigenotoxic response corresponded to 25.7, 63.1, and 75.5% at doses of 5, 50, and 500 mg/kg, respectively. Similarly, a statistically significant, dose-dependent decrease in genotoxicity (SCE's) was observed in MMS-treated mice after dosing with the crude oil. The 3 doses of crude oil tested (250, 500, and 1000 mg/kg) induced 24.8, 45.8, and 60.6% inhibition of genotoxicity, respectively.

Chamomilla Recutita (Matricaria) Tea Extract

Modification of the *in vitro* activity of heterocyclic aromatic amines [HAA, in DMSO] with the hot water extract of *Chamomilla recutita* (matricaria) tea was studied in the Ames plate incorporation test, with and without metabolic activation, using *Salmonella typhimurium* strain TA98.[85] Initially, measured volumes of the tea extract (usually 1, 5, 10, 50, and 100 µl) were plated in triplicate to establish a dose-response curve. DMSO served as the negative control, and there were 3 sets of positive controls, 2-amino-3- methylimidazo[4,5-*f*]quinolone (IQ), 2-amino-3,4-dimethylimidazo[4,5-*f*]quinolone (MeIQ), and B[*a*]P. Test results were expressed as the induced number of revertants by subtracting the number of spontaneous revertants (20-38 revertants/plate) from the total number obtained on each plate. A sample was considered mutagenic if it produced a dose-related increase in the number of revertants, when compared to the control, and if the number of revertants was at least 2.5 times greater than the spontaneous level. *Chamomilla recutita* (matricaria) tea (from flower heads) extract alone was not mutagenic.

HAAs were tested in combination with 2 doses of the tea extract, 10 and 50 mg tea leaves/plate (i.e., 10 and 50 milligram equivalents [mgEQ]). All tests were performed in triplicate. At both doses, *Chamomilla recutita* (matricaria) tea extract caused mild inhibition of the mutagenicity of IQ-type HAA (tested up to 0.5 ng/plate), but caused potentiation of the mutagenicity of 2-amino-3,7,8-trimethylimidazo[4,5-f]quinoxaline (7,8-DiMeIQx, tested at 5 ng/plate) and 4,7,8-TriMeIQx (tested at 10 ng/plate).[85]

CARCINOGENICITY

Carcinogenicity studies on the chamomile ingredients reviewed in this safety assessment were not found in the published literature, nor were unpublished studies provided.

Anticarcinogenicity

Chamomilla Recutita (Matricaria) Flower Extract

The cytotoxic activity of the following chamomilla recutita (matricaria) flower extracts against Yoshida ascites sarcoma was evaluated using Wistar Glaxo albino rats: 4.27% chamomilla recutita (matricaria) flower (petroleum ether extract), 10.04% chamomilla recutita (matricaria) flower (ethanol extract), and 13.73% chamomilla recutita (matricaria)

flower (distilled water extract).[86] The following procedure was followed prior to determining these 3 extract yields. Following filtration, the aqueous solutions were lyophilized or the organic solvents were removed in vacuo. The crude total extracts were then dissolved in phosphate buffer solution (pH 7.2) and sterilized by filtration. Ascites sarcoma cells were transplanted by i.p. injection into the rats. At 7 to 8 days post-injection, ascitic fluid was drawn from each animal, centrifuged, and the sediment was resuspended in the original volume with phosphate buffer solution. The tumor cells were then washed and resuspended in the same buffer solution to obtain a final concentration of 15×10^5/ml. Cytotoxicity was evaluated using the dye test. Equal volumes (0.2 ml) of serially diluted extracts (50 to 6.25 mg/ml) and of cell suspensions were mixed and incubated for 60 minutes. Trypan blue solution was then added to the mixture, and the differential count of stained and unstained cells was performed. Cytotoxicity was expressed as the LD_{50}. All 3 extracts were classified as exhibiting a poor cytotoxic effect ($LD_{50} > 10$ mg/ml).

Chamomilla Recutita (Matricaria) Flower Oil

The anticancer activity of chamomilla recutita (matricaria) flower oil against human leukemia HL-60 and NB4 cells was evaluated *in vitro* at concentrations up to 200 ppm.[87] The cells used were from human promyelocytic cell lines, and the oil was evaluated at concentrations of 25, 50, 75, 100, and 200 ppm in cells cultured for 24 h. Untreated cells served as controls. At the highest test concentration, the percentage of dead cells was 78.4% for HL-60 cells and 86.03% for NB4 cells.

BIOLOGICAL ACTIVITY

Immunomodulatory Activity

Chamomilla Recutita (Matricaria) Extract

The immunomodulatory activity of chamomilla recutita (matricaria) extract (extracted with methanol/water 50%) was studied using groups of 6 Balb/c mice.[88] The plant was grown in Egypt. Each of 6 animals was dosed i.p. with the extract (20 mg/dose/animal) for 5 consecutive days. Six untreated mice served as controls, and received the solvent (not stated) used to dissolve the extract. Blood samples were collected from the retro-orbital plexus. Dosing with the extract enhanced the total white blood cells count (up to 1.2×10^4 cells/mm^3). Bone marrow cellularity was also increased significantly ($P < 0.01$), and the same was true for spleen weight ($P < 0.01$). When 2 groups of mice were immunosuppressed with cyclophosphamide (200 mg/kg body weight), it was found that pretreatment of one of the groups with the extract restored the resistance of these mice against lethal fungal infection with the predominantly granulocyte-dependent *Candida albicans*. The results of this study confirmed the immunomodulatory activity of chamomilla recutita (matricaria) extract.

Chamomilla Recutita (Matricaria) Flower Oil

In another study, the efficacy of chamomilla recutita (matricaria) flower oil in alleviating atopic dermatitis-like immune alterations was evaluated using the following 4 groups of 10 BALB/c mice (7 weeks old):[89] normal group (saline applied throughout atopic dermatitis induction stage and oil treatment period), control group (saline applied following induction of atopic dermatitis), vehicle group (jojoba oil applied), and experimental group (3% chamomilla recutita (matricaria) flower oil applied after atopic dermatitis induction). Initially, the mice were sensitized twice per week with 1% 2,4-dinitrochlorobenzene (DNCB,100 µL), applied to dorsal skin (8 cm^2). During the following week, the animals were challenged twice with 0.2% DNCB (100 µL) for atopic dermatitis induction. Next, 3% chamomilla recutita (matricaria) flower oil (70 µL) was applied daily (6 times per week) for 4 weeks. Control mice were treated with saline or jojoba oil. Blood samples were collected following the second DNCB challenge and at 2 and 4 weeks after application of the oil.

When compared to the jojoba oil or saline control groups, the application of chamomilla recutita (matricaria) flower oil resulted in significant reduction ($p < 0.05$) of serum IgE levels at the end of the 4-week application period. When compared to 2 weeks of application (1.80 mg/mL reduction), 4 weeks of oil application caused a 31% (13.75 mg/mL) reduction in the serum IgG1 level. Additionally, when compared to the saline control group (37.43 ng/mL serum histamine level) or jojoba oil control group (30.60 ng/mL serum histamine level or 40% lower) at 2 weeks, application of the oil resulted in a significantly lower (18.45 ng/mL or 51% lower, $p < 0.05$) serum histamine level. The frequency of scratching following application of the oil was significantly lower when compared to either control group. The immunoregulatory potential of chamomilla recutita (matricaria) oil for alleviating atopic dermatitis through influencing of T helper 2 lymphocyte activation was demonstrated in this study.[89]

Wound Healing Activity

Chamomilla Recutita (Matricaria) Flower Extract

The wound healing activity of chamomilla recutita (matricaria) flower extract was evaluated using 2 groups of 6 Sprague-Dawley rats. [40] One group of rats received chamomilla recutita (matricaria) flower extract (aqueous extract) in drinking water at a dose of 120 mg/kg/day. The wound closure rate was assessed by tracing the wound on days 1, 5, 10, and 15 post-wounding. Epithelialization was said to have occurred when the eschar fell off without leaving a residual raw wound. Control rats were maintained on plain drinking water. Healing was assessed by the rate of wound contraction, period of epithelialization, wound-breaking strength, granulation tissue weight, and hydroxyproline content. When compared to controls on day 15, test animals had a greater reduction in wound area (61% - test; 48% - controls), faster epithelialization, and a statistically significantly higher wound-breaking strength ($p < 0.002$). Wet and dry granulation tissue weight and hydroxyproline content were also significantly higher in test animals. It was concluded that chamomilla recutita (matricaria) flower extract facilitated wound healing.

SUMMARY

The safety of German chamomile (*Chamomilla recutita* (*matricaria*))-derived ingredients is reviewed in this assessment. These ingredients function mostly as fragrance ingredients and skin conditioning agents in cosmetic products. The VCRP and Council survey data combined indicate that the following 8 chamomile ingredients have been used in cosmetic products: chamomilla recutita (matricaria) extract, chamomilla recutita (matricaria) flower, chamomilla recutita (matricaria) flower extract, chamomilla recutita (matricaria) flower/leaf extract, chamomilla recutita (matricaria) flower oil, chamomilla recutita (matricaria) flower powder, chamomilla recutita (matricaria) flower water, and chamomilla recutita (matricaria) oil. Of the ingredients reviewed in this safety assessment, the highest use concentration has been reported as 0.5% for chamomilla recutita (matricaria) flower.

Chamomilla recutita (matricaria) flower oil is produced by the steam distillation of chamomile (*Chamomilla recutita*) flowers. One of the trade name mixtures associated with chamomilla recutita (matricaria) flower extract [INCI name: mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract] is manufactured by prolonged maceration in a mixture of mineral oil and apricot kernel oil. Another trade name mixture associated with chamomilla recutita (matricaria) flower extract [INCI name: propylene glycol (and) water (and) chamomilla recutita (matricaria) flower extract] is manufactured by hydroglycolic extraction.

Sesquiterpenes, sesquiterpene alcohols (α-bisabolol, major component), and paraffin hydrocarbons are among the components of chamomilla recutita (matricaria) flower oil.

A UV spectral analysis has indicated an absorption maximum of 285 nm for chamomilla recutita (matricaria) flower oil. Additionally, a logP value of 5.29 has been reported for this ingredient.

In vivo data on the absorption, distribution, metabolism, and excretion of the *Chamomilla recutita*-derived cosmetic ingredients reviewed in this safety assessment were not found in the published literature. However, data relating to the absorption of and systemic exposure to bisabolol, a major component of chamomilla recutita (matricaria) flower oil, were considered. Using an *in vitro* membrane diffusion model, most of the components of chamomilla recutita (matricaria) oil, except for chamazulene, passed through the cellophane membrane.

The following ingredients did not induce acute toxicity when administered orally to mice or rats: chamomilla recutita (matricaria) flower (1,440 mg/kg), chamomilla recutita (matricaria) flower oil (5,000 mg/kg), and chamomilla recutita (matricaria) flower oil (5,600 mg/kg). The same was true for chamomilla recutita (matricaria) oil (5,000 mg/kg) when administered dermally to rabbits. Chamomile recutita (matricaria) flowers (in the form of herbal tea) did not induce oral toxicity when consumed repeatedly by rats or humans. Chamomilla recutita (matricaria) flower extract also did not induce oral toxicity in rats when administered repeatedly.

The antimicrobial activity of chamomilla recutita (matricaria) flower oil has been demonstrated using various bacterial and fungal strains.

Seven hay fever patients experienced conjunctivitis after ocular rinsing with *Chamomilla recutita* (matricaria) tea (from flowers). The results of a provocation test involving the tea extract confirmed that the tea induced allergic conjunctivitis. Chamomilla recutita (matricaria) flower oil was not irritating to the hen's egg chorioallantoic membrane in

the HET-CAM *in vitro* assay for assessing ocular irritation potential. The following trade name mixtures associated with chamomilla recutita (matricaria) flower extract were evaluated for ocular irritation in rabbits: mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract, propylene glycol (and) water (and) chamomilla recutita (matricaria) flower extract, and propylene glycol (and) water salvia officinalis (sage) leaf extract chamomilla recutita (matricaria flower extract). Each was classified as a non-irritant.

Skin irritation was observed in an acute dermal toxicity study on chamomilla recutita (matricaria) flower oil involving rabbits. Undiluted Chamomilla recutita (matricaria) flower oil was classified as non-irritating to the skin of hairless mice, and moderately irritating to the skin of rabbits. The following trade name mixtures associated with chamomilla recutita (matricaria) flower extract were evaluated for skin irritation in rabbits: mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract, propylene glycol (and) water (and) chamomilla recutita (matricaria) flower extract, and propylene glycol (and) water salvia officinalis (sage) leaf extract chamomilla recutita (matricaria flower extract). Each was classified as a non-irritant.

Cross-reactivity of 10% chamomilla recutita (matricaria) extract with carabron (a sesquiterpene lactone) was not demonstrated in a guinea pig skin sensitization study.

In a single application, epicutaeous patch test involving 29 normal subjects and 21 patients (17 with sensitive skin; 3 with eczema; 1 with allergy), results for a cuticle softener containing 0.3% chamomilla recutita (matricaria) flower extract were negative for skin irritation. In human predictive patch tests, chamomilla recutita (matricaria) flower oil (4%) was neither a skin irritant in subjects tested nor a skin sensitizer in a maximization test involving 25 subjects. Other predictive HRIPT results for a shave balm containing 0.2% chamomilla recutita (matricaria) flower extract (105 subjects), an eye lotion containing 0.4% chamomilla recutita (matricaria) flower extract (107 subjects), a facial cleansing and makeup remover towelettes containing 0.01% chamomilla recutita (matricaria) extract (50 subjects), and a hair gel styling mist containing 0.00006% chamomilla recutita (matricaria) flower/leaf extract (103 subjects) were negative for skin irritation and sensitization.

In provocative tests, skin sensitization was observed in 18 of 24 patients patch tested with 1% chamomilla recutita (matricaria) ether extract and in 4 of 5 patients and 48 of 85 patients patch tested with 2.5% chamomilla recutita (matricaria) ether extract in petrolatum. Five of 9 patients with positive patch test reactions to sesquiterpene lactone mix also had an allergic reaction to 2.5% *Chamomilla recutita* (matricaria) [plant part(s) not specified] in petrolatum. Skin sensitization was also observed in 19 gardeners and greenhouse workers with compositae-related symptoms who were patch tested with 2.5% *Chamomilla recutita* (matricaria) in petrolatum. Of 36 patients patch tested with ether extracts of *Chamomilla recutita* (matricaria), 30 had positive patch test reactions, most of which were ++ or +++. Similarly, of the 35 patients patch tested with 2.5% *Chamomilla recutita* (matricaria) in petrolatum, 22 had sensitization reactions (+ to +++). The number of patients (group of 35, sesquiterpene lactones mix sensitive) with positive reactions to chamomilla recutita (matricaria) flower aqueous extract decreased with decreasing test concentrations (100% [30 patients] to 1% [9 patients]). Of 129 patients (sensitive to compositae mix) patch-tested with 2.5% chamomilla recutita (matricaria) flower extract, 83 had sensitization reactions. In the prick test, chamomilla recutita (matricaria) extract (applied to forearm, 3.5 mg/ml) induced wheal formation in all 9 patients.

Provocative testing also yielded patch test reactions to chamomilla recutita flower oil, a doubtful positive reaction in 1 of 14 patients (4% concentration) and a ++ reaction to 4% and 1% in a second patient. Patch testing also resulted in a low incidence of skin sensitization to chamomilla recutita (matricaria) flower oil in 3 of 74 patients (2% in yellow soft paraffin), 2 of 200 patients, and 2 of 86 patients. The 86 patients were also sensitive to a perfume mixture. Positive reactions to chamomilla recutita (matricaria) flower extract and *Chamomilla recutita* plant parts (petals, leaves, flowers, and stems) were also observed in case reports.

Barely perceptible erythema was observed in hairless mice and miniature swine treated with chamomilla recutita (matricaria) flower oil in a photoxicity study, and these results were classified as negative. Photoaggravation was observed in 1 of 5 patients tested with 2.5% chamomilla recutita (matricaria) ether extract in a standard photopatch test.

For 37 regular users of chamomile (herbal product, genus and species not stated), both the frequency of threatening miscarriages and the frequency preterm labors were 21.6% higher when compared to non-users (group of 283); many of the subjects also consumed licorice.

The incidence of sister chromatid exchanges in bone marrow cells from mice dosed orally with chamomilla recutita (matricaria) flower extract was comparable to that observed in in bone marrow cells from control mice. The genotoxicity of one of the trade name mixtures associated with chamomilla recutita (matricaria) flower extract [mineral oil (and) prunus

armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract] was evaluated using the following bacterial strains: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2 *uvrA* pKM101. Results were negative both with and without metabolic activation. The antigenotoxic activity of chamomilla recutita (matricaria) flower oil and chamomilla recutita (matricaria) flower oil t was also demonstrated *in vitro*.

Carcinogenicity data on chamomile ingredients were not found in the published literature. Chamomilla recutita (matricaria) flower extract and chamomilla recutita flower oil caused a significant decrease in cell viability in human cancer cell lines.

Various biological effects of chamomile ingredients (*Chamomilla recutita (matricaria)*, such as immunomodulatory activity and wound healing activity, have been identified in the published literature.

DISCUSSION

Botanical ingredients, derived from natural plant sources, are complex mixtures. The Panel expressed concern that multiple botanical ingredients may each contribute to the final concentration of a single constituent. Azulene has been identified as a component of chamomilla recutita (matricaria) flower oil, and the Panel previously concluded that the available data are insufficient to support the safety of azulene for use in cosmetic products. The Panel also expressed concern over components of chamomilla recutita (matricaria) flower extract (i.e., quercetin, and quercetin-3-glucoside (isoquercitrin)) that may be genotoxic/carcinogenic, and components of chamomilla recutita (matricaria) flower oil (i.e., β-farnesene, linalool, and linalool acetate) that may be sensitizers (linalool and linalool acetate) and have insecticidal activity (β-farnesene). The Panel concluded that these components are not at levels of toxicologic concern in cosmetics, but also noted that, given the presence of *Chamomilla recutita*-derived ingredients in fragrances, plant constituents of toxicologic concern should not exceed any limitations that may have been established by the International Fragrance Association (IFRA). Thus, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse effects. The Panel also expressed concern about pesticide residues and heavy metals that may be present in *Chamomilla recutita*-derived ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities in the ingredient before blending into cosmetic formulations.

The Panel was concerned that cosmetics containing these ingredients be formulated to be non-sensitizing because the levels of potentially sensitizing constituents in the ingredients (e.g., sesquiterpene lactones), can be quite variable (depending on plant growth conditions, extraction methods, and other factors), and the data available from sensitization tests may not represent the complete spectrum of concentrations of such constituents in the ingredients as used in cosmetic products. In addition, the Panel was concerned that the concentrations of potentially sensitizing constituents should not exceed levels of concern in formulations containing ingredients from multiple plant species that each can contribute such constituents to the overall formulations.

In response to the Panel's request for skin irritation and sensitization data on chamomilla recutita (matricaria) flower extract, human repeated insult patch test (HRIPT) data on products containing 0.2%, 0.3%, and 0.4% chamomilla recutita (matricaria) flower extract were received. The 3 studies yielded negative results, and were considered sufficient, together with other skin sensitization data in the safety assessment, for evaluating the skin irritation and sensitization potential of all 5 *Chamomilla recutita* (matricaria) flower-derived ingredients in cosmetics. Current use concentration data received from the Personal Care Products Council indicate that *Chamomilla recutita* (matricaria) flower-derived ingredients are being used in leave-on products at concentrations up to 0.5% (chamomilla recutita (matricaria) flower extract), and the Panel agreed that the HRIPT data on products containing chamomilla recutita (matricaria) flower extract can be used to evaluate the safety of *Chamomilla recutita* (matricaria) flower-derived ingredients over the range of use concentrations reported. The Panel also considered that FDA has listed *Chamomilla recutita* flowers as generally recognized as safe (GRAS) for their intended use in food for human consumption. However, the Panel determined that the available data are insufficient for determining that ingredients derived from *Chamomilla recutita* leaf, and stem, or the whole plant are safe for use in cosmetics and that chemical composition data on these ingredients are needed.

Provocative patch testing involves patients with diseased skin. The Panel discussed the relevance of positive provocative test results for chamomilla recutita (matricaria) extract (ether extracts) at concentrations up to 2.5%, considering that the method of preparation of these extracts is dissimilar to those used to produce commercial *Chamomilla recutita*-derived ingredients. The commercial ingredients are produced by steam distillation or using multiple extraction solvents, such as oils, propylene glycol, water, and carbon dioxide, whereas, the ether extracts of freshly cut plants would probably

contain the maximally concentrated organic constituents. Therefore, the content of the ether extracts prepared specifically for the tests performed may deviate from the content of the commercially-supplied ingredients.

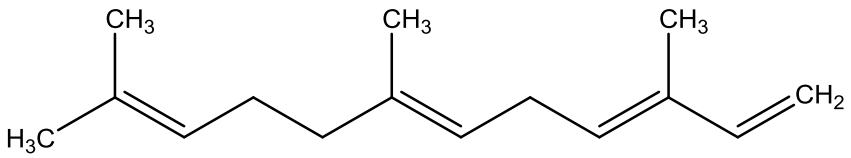
Because chamomilla recutita (matricaria) flower oil may contain (-)-α-bisabolol at concentrations as high as 41.45%, safety test data from the CIR final report on bisabolol are included in Table 1 of this safety assessment. The Panel concluded that bisabolol is safe as used in cosmetic formulations; reported use concentrations ranged from 0.001% to 1%. The following data on bisabolol are included in this report to support the safety of chamomilla recutita (matricaria) flower oil in cosmetic products: skin penetration, skin penetration enhancement, acute inhalation toxicity, acute oral and intraperitoneal toxicity, repeated dose oral and dermal toxicity, ocular irritation, skin irritation and sensitization, photosensitization, genotoxicity, and reproductive and developmental toxicity data.

The Panel discussed the issue of incidental inhalation exposure from propellant and pump hair sprays and face powders and sprays. Inhalation toxicity data were not available. However, the Panel considered pertinent data indicating that incidental inhalation exposures to these ingredients in such cosmetic products would not cause adverse health effects, including acute inhalation toxicity data on bisabolol and data characterizing the potential for these ingredients to cause acute and repeated dose oral toxicity, and ocular or dermal irritation or sensitization. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

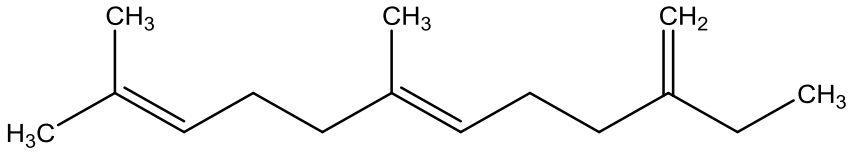
CONCLUSION

The CIR Expert Panel concluded that chamomilla recutita (matricaria) flower, chamomilla recutita (matricaria) flower extract, chamomilla recutita (matricaria) flower powder, chamomilla recutita (matricaria) flower water, chamomilla recutita (matricaria) flower oil are safe in the present practices of use and concentration, described in this safety assessment, in cosmetics, when formulated to be non-sensitizing. The Panel also concluded that the available data are insufficient to make a determination that chamomilla recutita (matricaria) extract, chamomilla recutita (matricaria) flower/leaf extract, chamomilla recutita (matricaria) flower/leaf/stem extract, chamomilla recutita (matricaria) flower/leaf/stem water, chamomilla recutita (matricaria) leaf extract, and chamomilla recutita (matricaria) oil are safe under the intended conditions of use in cosmetics.

1. Farnesene

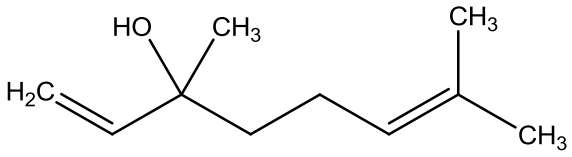


alpha-farnesene

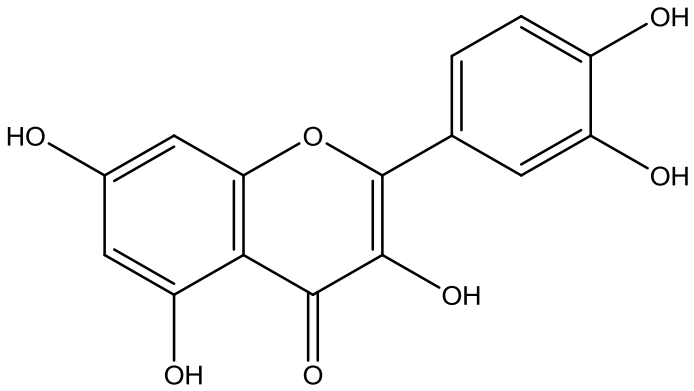


beta-farnesene

2. Linalool



3. Quercetin



4. Azulene

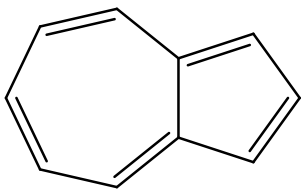


Figure 1. Structural formulas for some of the constituents of chamomilla recutita (matricaria) flower oil and extract.

Table 1. Data from CIR Final Safety Assessment on Bisabolol

Test Substance	Animals/Subjects/ Tissues/Cells Studied	Procedure	Results
		Skin Penetration Enhancement	
1:1 α-Bisabolol:propylene glycol mixture	Epidermis from abdominal human cadaver skin	Pretreatment of epidermis with test substance, followed by application of 5-fluorouracil (5-FU) or triamcinolone acetonide.	Increased permeability of 5-FU and triamcinolone acetonide by 17- and 73-fold, respectively.[90]
α-Bisabolol	Epidermis from abdominal human cadaver skin	Pretreatment of epidermis with test substance, followed by application of 5-FU.	5-fold increase in 5-FU permeability. α-Bisabolol altered the transition enthalpy of skin lipids.[90]
		Skin Penetration	
^{14}C-Levomenol [(-)-6-methyl-2-(4-methyl-3-cyclohexen-1-yl)-5-hepten-2-ol and (-)-α-Bisabolol]	Mice (number and strain not specified)	^{14}C-Levomenol solution, delivered with either arlatone or acetone as a solubilizer, applied to shaved skin (radioactive dose = 40.6 kBq).	After 1 h, 80% of applied radioactivity (from arlatone solution) remained at application site. By 3 h and 5 h, radioactivity at application site decreassed to 57% and 50%, respectively. Similar results with acetone solution. ^{14}C-Levomenol detected in fatty and muscle tissues of the neck.[91]
		Acute Oral Toxicity	
(-)-α-Bisabolol	Mice (number and strain not specified)	Oral dosing (procedure not stated)	LD_{50} = 15.1 ml/kg.[92]
(-)-α-Bisabolol	Rats (number and strain not stated)	Oral dosing (procedure not stated)	LD_{50} = 15.6 ml/kg (females) and 14.9 ml/kg (males).[92]
(±)-α-Bisabolol	Rats (number and strain not stated)	Oral dosing (procedure not stated)	LD_{50} > 5 g/kg.[93]
		Acute Parenteral Toxicity	
(±)-α-Bisabolol	12 rats (strain not stated)	Exposed for 7 h to aerosolized test substance.	No deaths or lesions at necropsy.[94]
(±)-α-Bisabolol (in emulsion)	Mice (number and strain not specified)	Intraperitoneal dosing	LD_{50} = 633 mg/kg.[95]
		Repeated Dose Toxicity	
Bisabolol (85% pure oily liquid)	Groups of 20 Wistar Br 46-II rats (10 per sex)	1 ml/kg by stomach tube 7 days/week for 6 weeks.	No intolerance reactions observed.[92]
Bisabolol (85% pure oily liquid)	2 groups of 40 Sprague-Dawley rats (20 per sex)	2 ml/kg or 3 ml/kg by stomach tube 7 days/week for 4 weeks.	Slight and increased motor agitation at 2 ml/kg and 3 ml/kg, respectively; 20% mortality and decreased body weight gain at 3 ml/kg. Inflammatory changes (more severe at 3 ml/kg) in liver, trachea, spleen, thymus, and stomach; characterized as an"infection defense weakness triggered by the emaciation".[92]
Bisabolol (85% pure oily liquid)	2 mixed breed dogs	1 ml/kg body weight by stomach tube 7days/week for 2 weeks.	No intolerance reactions observed. [92]
Bisabolol (85% pure oily liquid)	Groups of 6 dogs (3 per sex)	2 ml/kg or 3 ml/kg (increased to 4 ml/kg at week 2) oral dose 7 days/week for 4 weeks.	Appetite loss and reduced feed intake at 2 ml/kg; both more severe at 4 ml/kg. At necropsy, liver weight-relative-to-body-weight significantly increased.[92]

Table 1. Data from CIR Final Safety Assessment on Bisabolol

Test Substance	Animals/Subjects/ Tissues/Cells Studied	Procedure	Results
α-Bisabolol (87.5% pure, in olive oil)	10 Wistar rats (5 per sex)	Applied to clipped skin (under semiocclusive dressing) at doses of 50, 200, and 1000 mg/kg body weight. Doses applied 7 days/week (6 h/day) for 4 weeks.	No treatment-related effects in low- and mid-dose groups. Slight decrease in body weight gain and feed efficiency in all rats of high-dose group only on day 7; also, decreased mean terminal body weight (high-dose males and females). High-dose female rats also had transient, moderate erythema. NOAEL = 200 mg/kg/day.[96]
		Ocular Irritation	
(-)-α-Bisabolol (undiluted)	3 rabbits	Instilled into 1 conjunctival sac of each animal; eyes not rinsed.	Well-defined conjunctival redness in all rabbits at 1 h, 24 h, and 48 h, but not at 72 h.[97]
		Skin Irrritation and Sensitization	
(-)-α-Bisabolol (undiluted)	3 white Vienna rabbits	Semiocclusive patches with test substance applied for 4 h to clipped back or flank.	At 4 h reading, very slight erythema in all rabbits. Well-defined erythema in 2 rabbits at 24 h, and very slight erythema in 1 rabbit at 72 h.[98]
Bisabolol (5% in petrolatum)	Patients (total number not stated) suffering from or suspected of suffering from cosmetic product contact allergy	Patch test (procedure not stated)	No skin irritation in 1 to 20 patients. According to source, these preliminary results were from an unpublished, ongoing study.[99]
Product containing 0.1% bisabolol	25 panelists	Maximization test (occlusive patches)	Neither irritation nor sensitization observed.[100]
		Photosensitization	
Bisabolol (3% or 15% v/v in absolute alcohol or olive oil)	Groups of 5 male white Pirbright guinea pigs	Test substance (in absolute alcohol) applied to shaved skin of neck. Application followed by irradiation with light at 240-540 nm wavelengths (7.9 kilolumens for 15 min). Protocol followed for 5 days, then a 9-day non-treatment period. Protocol then repeated (vehicle changed to olive oil) for 2 successive days, followed by 12-day non-treatment period. Bisabolol solutions (dissolved in commercial soap) then applied to left leg, followed by irradiation, and procedure repeated for 3 days.	No evidence of photosensitization.[101]
		Genotoxicity	
Bisabolol (86.8% pure, in DMSO)	*Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537	Ames standard plate test (doses up to 5,000 µg/plate); preincubation protocol (doses up to 1,500 µg/plate). Both protocols with and without metabolic activation.	Non-genotoxic in both assays.[102]
Bisabolol (86.8% pure, in DMSO)	Chinese hamster V79 cells	Chromosome aberrations assay. Doses up to 31.25 µg/ml (with metabolic activation) and up to 3.13 µg/ml (without metabolic activation).	Non-genotoxic.[103]
Bisabolol (86.8% pure, in DMSO)	Chinese hamster V79 cells	Chromosome aberrations assay. Doses up to 40 µg/ml (with metabolic activation) and up to 4 µg/ml (without metabolic activation).	Non-genotoxic.[103]

Table 1. Data from CIR Final Safety Assessment on Bisabolol

Test Substance	Animals/Subjects/ Tissues/Cells Studied	Procedure	Results
		Reproductive and Developmental Toxicity	
Bisabolol (98% pure)	Pregnant rats (number and strain not stated)	Oral (stomach tube) doses up to 3.0 ml/kg body weight on days 6-15 of gestation.	No effect on prenatal development at doses ≤ 1.0 ml/kg. Significant reduction in fetal number and subsequent increase in resorption rate at 3.0 ml/kg. No deformities observed. Lowest toxic dose for both fetuses and dams between 1 and 3 ml/kg body weight perorally.[92]
Bisabolol	Pregnant New Zealand rabbits (number not stated)	Oral (stomach tube) doses up to 3.0 ml/kg body weight on days 6-15 of gestation.	No effect on prenatal development at doses ≤ 1.0 ml/kg. Reduction in number of living fetuses at 3.0 ml/kg; no deformities or dead fetuses. Lowest toxic dose for both fetuses and dams between 1 and 3 ml/kg body weight perorally.[92]

Table 2. Definitions and functions of the ingredients in this safety assessment[1]

Ingredient, CAS No.	Definition	Function
Chamomilla Recutita		
Chamomilla Recutita (Matricaria) Extract	Chamomilla Recutita (Matricaria) Extract is the extract of the whole plant, *Chamomilla recutita.*	Skin-conditioning agents-miscellaneous
Chamomilla Recutita (Matricaria) Flower	Chamomilla Recutita (Matricaria) Flower is the flower of *Chamomilla recutita*.	Skin-conditioning agents-miscellaneous
Chamomilla Recutita (Matricaria) Flower Extract [84082-60-0]	Chamomilla Recutita (Matricaria) Flower Extract is the extract of the flowerheads of the matricaria, *Chamomilla recutita.*	Fragrance ingredients; skin-conditioning agents-miscellaneous; skin conditioning agents-occlusive
Chamomilla Recutita (Matricaria) Flower/Leaf Extract	Chamomilla Recutita (Matricaria) Flower/Leaf Extract is the extract of the flowers and leaves of *Chamomilla recutita.*	Cosmetic Biocides
Chamomilla Recutita (Matricaria) Flower/Leaf/Stem Extract	Chamomilla Recutita (Matricaria) Flower/Leaf/Stem Extract is the extract of the leaves, flowers and stems of *Chamomilla recutita.*	Flavoring agents; oral care agents; skin conditioning agents-miscellaneous
Chamomilla Recutita (Matricaria) Flower/Leaf/Stem Water	Chamomilla Recutita (Matricaria) Flower/Leaf/Stem Water is an aqueous solution of the steam distillate obtained from the flowers, leaves and stems of *Chamomilla recutita.*	Fragrance ingredients
Chamomilla Recutita (Matricaria) Flower Oil [8002-66-2]	Chamomilla Recutita (Matricaria) Flower Oil is the volatile oil obtained from the flowers of *Matricaria recutita*.	Fragrance ingredients; skin-conditioning agents-miscellaneous
Chamomilla Recutita (Matricaria) Flower Powder	Chamomilla Recutita (Matricaria) Flower Powder is the powder obtained from the dried, ground flowers of *Chamomilla recutita.*	Skin-conditioning agents-miscellaneous
Chamomilla Recutita (Matricaria) Flower Water	Chamomilla Recutita (Matricaria) Flower Water is an aqueous solution of the steam distillate obtained from the flowers of *Chamomilla recutita*.	Fragrance ingredients
Chamomilla Recutita (Matricaria) Leaf Extract [84082-60-0]	Chamomilla Recutita (Matricaria) Leaf Extract is the extract of the leaves of *Chamomilla recutita.*	Fragrance ingredients; skin-conditioning agents-miscellaneous
Chamomilla Recutita (Matricaria) Oil	Chamomilla Recutita (Matricaria) Oil is the volatile oil obtained from the whole plant, *Chamomilla recutita.*	Fragrance ingredients

Table 3. Chemical and Physical Properties[38,104]

Properties	Chamomilla Recutita (Matricaria) Flower Oil
Form	Deep blue or blue-green liquid with strong, characteristic odor
logP	5.29
Specific gravity	Between 0.910 and 0.950
Solubility	Soluble in most fixed oils and in propylene glycol. Insoluble in glycerin and in mineral oil
Acid value	Between 5 and 50 mg KOH/g oil
Ester value	Between 65 and 155 KOH/g oil
Saponification number	≈ 43
UV absorption maximum	285 nm

Table 4.Composition Data on *Chamomilla Recutita* (Matricaria) Trade Name Materials.[10]

Trade Name	INCI Name	Composition (%)	Extraction Solvent
Vegetol matricaria 4140 oily	Mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) flower extract	> 75.0, 10 to 24.9, and 1 to 4.9, respectively	Mineral oil and prunus armeniaca (apricot) kernel oil
Vegetol matricaria GR 337 Hydro	Butylene glycol (and) water (and) chamomilla recutita (matricaria) flower extract	> 50, 25 to 0, and 5 to 9.9, respectively	Butylene glycol and water
Vegetol matricaria MCF 793 hydro	Propylene glycol (and) water (and chamomilla recutita (matricaria) flower extract	50.0 to 75.0, 25 to 50, and 5 to 9.9, respectively	Propylene glycol and water
Vegetol matricaria ME 106 hydro	Propylene glycol (and) water and chamomilla recutita (matricaria) flower extract	>50, 25 to 50, and 5 to 9.9, respectively	Propylene glycol and water
Vegetol SP GR 051 hydro	Propylene glycol and water, salvia officinalis (sage) leaf extract,and chamomilla recutita (matricaria) flower extract	25 to 50, 25 to 50, 1 to 4.9, and 0.1 to 0.9, respectively	Propylene glycol and water

Table 5. Composition of Chamomilla Recutita Ingredients.[4,5,19,38,105,106,107,108,109,110]

Data	Ingredients		
Components/Impurities	**Chamomilla Recutita (Matricaria) Flower Extract**	**Chamomilla Recutita (Matricaria) Flower Oil**	**Chamomilla Recutita (Matricaria) Flower**
Apigenin	3.0 to 95.1 µmol/l		6 to 8400 ppm
Apigenin-7-glucoside	94.1 to 216.2 µmol/l		
Artemesia alcohol		< 0.1% to 0.2%	
Artemisia ketone		< 0.1 to 7.8%	
Azulene		0.40%	
Benzaldehyde		< 0.1%	
Benzyl alcohol		< 0.1%	
cis-En-yn-bicycloether		3.6 to 17.7%	
Bicyclogermacrene		0.10%	
β-Bisabolenal		0.80%	
cis-α-Bisabolene		0.30%	
cis-α-Bisabolene epoxide		< 0.05% to 3.8%	
α-Bisabolene oxide A		1.31 to 10%	
β-Bisabolene		0.2 to 19.6%	
(Z)-γ-Bisabolene		0.50%	
trans-γ-Bisabolene		0.10%	
Bisabolol			600 to 5,000 ppm
α-Bisabolol		0.7 to 13.15%	725 to 10,000 ppm
(-)-α-Bisabolol		1.59 to 41.45%	
α-Bisabolol acetate		1.80%	
α-Bisabolol oxide A		< 0.05% to 55.9%	
Bisabolol-oxide A		0.42 to 36.27%	
Bisabolol oxide B		4.64% to 11.17%	
α-Bisabolol oxide B		1.2 to 25.1%	
β-Bisabolol		0.1 to 2.5%	
Bisabolone-oxide		0.55 to 4.13%	
α-Bisabolone oxide A		< 0.05% to 13.6%	
Borneol		0.80%	
Butyl phthalate		15.10%	
Cadina-1,4-diene		< 0.1%	
α-Cadinene		0.2 to 3.75%	
δ-Cadinene		0.1 to 5.20%	
γ-Cadinene		0.1 to 2.25%	
Caffeic acid	1.2 to 5.1 µmol/l		
α-Calacorene		< 0.1%	
trans-Calamenene		< 0.1%	
Camphor		≤ 0.1%	
trans-Carveol		0.10%	

Table 5. Composition of Chamomilla Recutita Ingredients.[4,5,19,38,105,106,107,108,109,110]

Data	Ingredients		
Components/Impurities	**Chamomilla Recutita (Matricaria) Flower Extract**	**Chamomilla Recutita (Matricaria) Flower Oil**	**Chamomilla Recutita (Matricaria) Flower**
β-Caryophyllene		< 0.1 to 0.9%	
Caryophyllene oxide		0.70%	
Chamazulene		0.2 to 24.50%	530 to 13,200 ppm
Chamo-spiroether		4.71%	
Chlorogenic acid	7.3 to 310.3 µmol/l		
Choline			3,400 to 3,800 ppm
cis-Chrysanthenol		0.10%	
1,8-Cineole		< 0.1% to 2.1%	
α-Copaene		0.2% to 0.24%	
ar-Curcumene		< 0.1%	
p-Cymene		0.05% to 1.1%	
para-Cymene-8-ol		0.70%	
Daucene		0.50%	
Decanoic acid		0.3 to 3.7%	
Dendrolasin		0.50%	
trans-Dicycle-ether		3.20%	
2,4-Dihydroxybenzoic Acid	Amount not stated	Amount not stated	Amount not stated
2,5-Dihydro-2,5-dimethylfuran		< 0.1%	
2,6-Dimethyl-5-heptenal		< 0.1%	
β-Elemene		< 0.1% to 0.9%	
δ-Elemene		0.10%	
γ-Elemene		0.70%	
Essential Oil (EO)			2,400 to 20,000 ppm
Ethyl decanoate		< 0.1%	
Ethyl hexanoate		< 0.1%	
Ethyl 2-methybutyrate		< 0.1%	
ethyl isovalerate		< 0.1%	
γ-Eudesmol		1.50%	
α-Farnesene		0.15 to 27.72%	
(*E*,*E*)-α-Farnesene		3.10%	
β-Farnesene		52.30%	
(E)-β-Farnesene		0.9 to 10.9%	
cis-β-farnesene		0.90%	
tr-β-Farnesene		7.2 to 12.8%	
trans-β-Farnesene		5.20%	
(Z)-β-Farnesene		< 0.1% to 15.97%	
Furfural		< 0.1%	
Galactose			150,000 ppm
Galacturonic Acid			750,000 ppm
Geraniol		< 0.1%	

Table 5. Composition of Chamomilla Recutita Ingredients.[4,5,19,38,105,106,107,108,109,110]

Data	Ingredients		
Components/Impurities	**Chamomilla Recutita (Matricaria) Flower Extract**	**Chamomilla Recutita (Matricaria) Flower Oil**	**Chamomilla Recutita (Matricaria) Flower**
Germacrene-D		0.16 to 5.78%	
Glucose			70,000 ppm
2-Heptanone		< 0.1%	
Herniarin			320 to 915 ppm
Hexadecanoic acid		0.3 to 23%	
Hexanal		< 0.1%	
(Z)-3-Hexanol		0.10%	
(E)-2-Hexenal		< 0.1%	
(E)-β-Ionone		0.10%	
Isorhamnetin	0.1 to 3.6 µmol/l		
Juniperol		0.90%	
Kaempferol	0.2 to 0.9		
Ledol		< 0.1%	
Limonene		0.1% to 0.2%	
Linalool		0.10%	
Linalool acetate (dihydro)		3.39%	
cis-Linalool oxide (furanoid)		< 0.1%	
trans-Linalool oxide (furanoid)		< 0.1%	
cis-Linoleic acid		< 0.05% to 11.9%	
Luteolin	0.6 to 9.2 µmol/l		
Methyl decanoate		< 0.1%	
Methyl guaiacol		< 0.1%	
6-Methyl-5-hepten-2-ol		< 0.1%	
6-Methyl-5-hepten-2-one		0.10%	
Methyl hexadecanoate		2.60%	
5-Methyl-2-hexanal		< 0.1%	
Methyl linoleate		1.00%	
Methyl linolenate		1.10%	
Mucilage			100,000 ppm
α-Muurolene		0.8 to 3.41%	
γ-Muurolene		1.31%	
α-Muurolol		0.30%	
Myrcene		< 0.1%	
(E)-Nerolidol		0.20%	
Nonanal		< 0.1%	
n-Nonanal		0.10%	
Nonanoic acid		0.30%	
3-Nonen-2-one		< 0.1%	
(E)-β-Ocimene		0.10%	
(Z)-β-Ocimene		0.20%	

Table 5. Composition of Chamomilla Recutita Ingredients.[4,5,19,38,105,106,107,108,109,110]

Data	Ingredients		
Components/Impurities	**Chamomilla Recutita (Matricaria) Flower Extract**	**Chamomilla Recutita (Matricaria) Flower Oil**	**Chamomilla Recutita (Matricaria) Flower**
trans-β-Ocimene		1.73%	
(E,E)-3,5-Octadien-2-one		< 0.1%	
Octanal		< 0.1%	
2-Octanol		< 0.1%	
3-Octanol		< 0.1%	
1-Octen-3-ol		< 0.1%	
3-Octen-2-one		< 0.1%	
2-Phenylethanol		0.20%	
α-Pinene		< 0.1% to 0.12%	
β-Pinene		< 0.1%	
Pinocarvone		< 0.1%	
Quercetin	0.5 to 6.5 µmol/l		
Quercetin-3-glucoside	1.7 to 10.6 µmol/l		
Quercitrin	limit of detection		
Rutin	0.7 to 2.9 µmol/l		
cis-Sabinene hydrate		0.20%	
Sabinene		< 0.1%	
Safrole		< 0.1%	
Salicylates			0.6 ppm
Salvial-4(14)-en-1-one		0.1 to 4.1%	
(Z)-β-Santalol		1%	
β-Selinene		1%	
Spathulenol		0.46 to 9.4%	
Spiroether		1.10%	
cis-Spiroether		3.43 to 7.48%	
cis-en-yn-Spiroether		0.73%	
trans-Spiroether		0.9 to 6.01%	
Terpinen-1-ol		< 0.1%	
Terpinen-4-ol		< 0.1%	
γ-Terpinene		< 0.1% to 0.3%	
α-Terpineol		0.10%	
4-Terpineol		0.10%	
α-Thujone		< 0.1%	
2,2,6-Trimethylhexanone		< 0.1%	
Umbelliferone	1.0 to 53.1 µmol/l		20 to 290 ppm
α-Ylangene		< 0.1%	
Yomogi alcohol		< 0.1%	

Table 6. Frequency and Concentration of Use According to Duration and Type of Exposure[22,23]

	Chamomilla Recutita (Matricaria) Extract		**Chamomilla Recutita (Matricaria) Flower**		**Chamomilla Recutita (Matricaria) Flower Extract**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	2	0.0001-0.4	1	NR	58	0.0001-0.2
Incidental Ingestion	NR	0.002	NR	NR	3	0.0002-0.5
Incidental Inhalation- Sprays	NR	0.1	NR	0.02	115	0.00001-0.01
Incidental Inhalation- Powders	1	0.0004	NR	NR	20	NR
Dermal Contact	4	0.0001-0.61	1	NR	700	0.000025-0.2
Deodorant (underarm)	NR	NR	NR	NR	3	NR
Hair - Non-Coloring	2	NR	NR	0.02-0.5	234	0.00001-0.25
Hair-Coloring	NR	NR	NR	0.02-0.3	20	0.00001-0.02
Nail	NR	NR	NR	NR	7	0.002-0.3
Mucous Membrane	NR	0.002-0.61	1	NR	100	0.000025-0.5
Baby Products	1	NR	NR	NR	26	0.0097
Duration of Use						
Leave-On	4	0.0001-0.4	1	0.02	507	0.00001-0.5
Rinse off	2	0.01-0.61	NR	0.02-0.5	440	0.00001-0.25
Diluted for (bath) Use	NR	NR	NR	NR	19	0.0051
Totals/Conc. Range	6	0.0001-0.61	2	0.02-0.5	966	0.00001-0.5
	Chamomilla Recutita (Matricaria) Flower/Leaf Extract		**Chamomilla Recutita (Matricaria) Flower Oil**		**Chamomilla Recutita (Matricaria) Flower Water**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	9	NR	6	0.001	1	NR
Incidental Ingestion	1	0.01	4	0.03	NR	NR
Incidental Inhalation- Sprays	100	0.0001	12	0.007-0.066	NR	NR
Incidental Inhalation- Powders	4	0.002	3	NR	NR	NR
Dermal Contact	251	0.002-0.02	93	0.0001-0.2	11	NR
Deodorant (underarm)	1	NR	NR	NR	NR	NR
Hair - Non-Coloring	89	0.0001	28	0.007-0.1	NR	NR
Hair-Coloring	6	NR	NR	0.06	NR	NR
Nail	NR	0.01	NR	NR	NR	NR
Mucous Membrane	37	0.01	34	0.0001-0.03	1	NR
Baby Products	5	NR	5	NR	NR	NR
Duration of Use						
Leave-On	218	0.0001-0.02	67	0.001-0.2	9	NR
Rinse off	127	NR	49	0.0001-0.06	2	NR
Diluted for (bath) Use	4	NR	9	NR	NR	NR
Totals/Conc. Range	349	0.0001-0.02	125	0.0001-0.2	11	NR
	Chamomilla Recutita (Matricaria) Flower Powder		**Chamomilla Recutita (Matricaria) Oil**			
	# of Uses	Conc. (%)	# of Uses	Conc. (%)		
Exposure Type						
Eye Area	NR	NR	1	NR		
Incidental Ingestion	NR	NR	NR	NR		
Incidental Inhalation- Sprays	NR	NR	NR	NR		
Incidental Inhalation- Powders	NR	NR	NR	NR		
Dermal Contact	NR	1	8	NR		
Deodorant (underarm)	NR	NR	NR	NR		
Hair - Non-Coloring	NR	NR	3	NR		
Hair-Coloring	NR	NR	NR	NR		
Nail	NR	NR	NR	NR		
Mucous Membrane	NR	NR	NR	NR		
Baby Products	NR	NR	NR	NR		
Duration of Use						
Leave-On	NR	NR	10	NR		
Rinse off	NR	1	1	NR		
Diluted for (bath) Use	NR	NR	NR	NR		
Totals/Conc. Range	NR	1	11	NR		

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure Provided in 2013

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

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