Safety Assessment of
Anthemis Nobilis-Derived Ingredients as Used in Cosmetics

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<tr>
<th>Status:</th>
<th>Tentative Report for Panel Review</th>
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<tr>
<td>Release Date:</td>
<td>September 23, 2013</td>
</tr>
<tr>
<td>Panel Date:</td>
<td>December 9-10, 2013</td>
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All interested persons are provided 60 days from the above release date to comment on this Safety Assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. Lillian J. Gill.

The 2013 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A. Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.
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ABSTRACT: Anthemis nobilis flower extract, anthemis nobilis flower oil, anthemis nobilis flower powder, and anthemis nobilis flower water are ingredients that function as fragrance ingredients and skin conditioning agents in cosmetic products. Three ingredients are being used at concentrations up to 10% (anthemis nobilis flower water) in cosmetic products. The available data indicate that these 4 ingredients are not irritating or sensitizing. Chemical composition data and the low use concentrations suggest that systemic toxicity would not be likely if percutaneous absorption of constituents were to occur. Formulations may contain more than one botanical ingredient; each may contribute to the final concentration of a single component. Manufacturers were cautioned to avoid reaching levels of plant constituents that may cause sensitization or other adverse effects. Industry should continue to use good manufacturing practices to limit impurities in the ingredient before blending into cosmetic formulations. The Expert Panel concluded that these ingredients are safe in the present practices of use and concentration in cosmetics, when formulated to be non-sensitizing.

INTRODUCTION

This tentative report presents information relevant to evaluating the safety of the following 4 Roman chamomile or Anthemis nobilis-derived ingredients as used in cosmetics: anthemis nobilis extract, anthemis nobilis flower oil, anthemis nobilis flower powder, and anthemis nobilis flower water. The Cosmetic Ingredient Review (CIR) is evaluating 11 Chamomilla recutita (German chamomile) derived ingredients in a separate report because the CIR Expert Panel thought that these two groups of botanical ingredients were substantially different and should not be addressed in the same report. These Anthemis nobilis-derived ingredients function as fragrance ingredients and skin conditioning agents in cosmetic products.

CHEMISTRY

The plant source of the ingredients reviewed in this safety assessment is Anthemis nobilis L. [Asteraceae]. Compositae family is the previous or historical name for the Asteraceae family. Chamaemelum nobile is a synonym for Anthemis nobilis. The definitions of the 4 chamomile ingredients presented in this safety assessment are included in Table 1.

Physical and Chemical Properties

Anthemis nobilis flower oil is a light blue or light blue-green liquid with a specific gravity of between 0.892 and 0.910 (Table 2). Information on the remaining 3 ingredients was not found, nor was unpublished information provided.

Method of Manufacture

Anthemis Nobilis Flower Oil

The preparation of anthemis nobilis flower oil reportedly involves the steam distillation of the dried flowers of Anthemis nobilis as a key step.

Composition/Impurities

A trade name material containing anthemis nobilis flower extract consists of the flower extract in propylene glycol and water (Table 3). Heavy metals and other components have been reported in anthemis nobilis flower oil, and the Anthemis nobilis plant and its flower (Table 4).

Anthemis Nobilis Flower Oil

According to the Personal Care Products Council (Council), the chamomile essential oil tested in the 2 skin irritation and sensitization studies summarized later in this report was derived from Anthemis nobilis L. The results of an analysis of this oil are included below:

- isobutyl angelate (30% to 35%)
- 2-methylbutyl angelate (15% to 20%)
- methallyl angelate (5% to 10%)
- isobutyl isobutyrate (5% to 10%)
- pinocarveol (1% to 5%)
- isoamyl angelate (1% to 5%)
• alpha-pinene (1% to 5%)
• unknown 71/43/100 mw = 170 (1% to 5%)
• pentan-2-yl butyrate (% to 5%)
• butyl methacrylate, iso-(2-propenoic acid, 2-methyl:isobutyl ester) (% to 5%)
• angelyl angelate (1% to 5%)
• propyl angelate (1% to 5%)

Results from the nutritional characterization of *Anthemis nobilis* are stated as follows: Carbohydrates are the most abundant macronutrients, followed by proteins. Ash and fat contents were low, and the energetic contribution was 389.88 kcal/100 g dry weight. The main sugar found in *Anthemis nobilis* was fructose, followed by glucose and sucrose. Trehalose was found in lower amounts. Polyunsaturated fatty acids (PUFA) predominated over saturated fatty acids (SFA) and monounsaturated fatty acids (MUFA). The fatty acids determined in higher percentages were linoleic acid (C18:2n6), oleic acid (C18:1n9), α-linolenic acid (C18:3n3), and palmitic acid (C16:0). Regarding tocopherols, only α- and γ-tocopherols were found in *Anthemis nobilis*. β-Carotene and lycopene were also quantified in the sample studied.

**USE**

**Cosmetic**

The *Anthemis nobilis* ingredients function as fragrance ingredients and skin conditioning agents in cosmetic products.

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. The Council conducted a survey of ingredient use concentrations in 2013, indicating use at concentrations up to 10% (anthemis nobilis flower water).

As shown in Table 5, both VCRP use data and use concentration data were available for the following 3 ingredients:

• anthemis nobilis flower extract
• anthemis nobilis flower oil
• anthemis nobilis flower water

Neither VCRP data nor use concentration data were available for:

• anthemis nobilis flower powder

Cosmetic products containing *Anthemis nobilis*-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 reported maximum use concentration = 2.8% anthemis nobilis flower oil in a potential spray product [perfume]): anthemis nobilis flower extract, anthemis nobilis flower oil, and anthemis nobilis flower water. Because these ingredients are used in products that are sprayed, 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. 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.
Non-Cosmetic

*Anthemis nobilis* (Roman 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. 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.

*Anthemis nobilis* 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. 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.

FDA has determined that the available data are inadequate for establishing general recognition of safety and effectiveness of chamomile flowers as used in digestive aid drug products.

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. 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*).

**TOXICOKINETICS**

Data on the absorption, distribution, metabolism, and excretion of *Anthemis nobilis* flower extract, *Anthemis nobilis* flower oil, *Anthemis nobilis* flower powder, or *Anthemis nobilis* flower water were not found in the published literature, nor were unpublished data provided.

**TOXICOLOGY**

**Acute Toxicity**

**Oral**

*Anthemis Nobilis Flower Oil*

The acute oral toxicity of *Anthemis nobilis* flower oil (dose = 5 g/kg) was evaluated using 10 rats (strain not stated). Dosing was followed by a 14-day observation period. None of the animals died, and an LD$_{50}$ of > 5 g/kg was reported.

**Ocular Irritation**

*Anthemis Nobilis Flower Extract*

One of the trade name mixtures associated with *Anthemis nobilis* flower extract has the INCI name, propylene glycol (and) water (and) *Anthemis nobilis* flower extract and contains 5%-9.9% *Anthemis nobilis* flower extract (Table 3). It is also known as Vegetol® chamomile LC 376 hydro, and the extraction solvent is propylene glycol and water. The ocular irritation potential of this trade name mixture was evaluated using 6 New Zealand hybrid albino male rabbits. The mixture (20% (v/v) solution in distilled water; volume = 0.1 ml) was instilled into the inferior conjunctival sac of the right eye. Reactions were scored 1 h post-instillation and then 1, 2, 4, and, possibly, 7 days post-instillation. The diluted mixture was classified as a very slight ocular irritant.
Skin Irritation

Animal

Anthemis Nobilis Flower Extract

One of the trade name mixtures associated with anthemis nobilis flower extract has the INCI name, propylene glycol (and) water (and) anthemis nobilis flower extract and contains 5%-9.9% anthemis nobilis flower extract (Table 3). It is also known as Vegetol® chamomile LC 376 hydro, and the extraction solvent is propylene glycol and water. The skin irritation potential of this mixture (20% v/v solution in distilled water) was evaluated using 6 New Zealand hybrid albino male rabbits.21 The trade name mixture was applied to intact and scarified skin sites (on clipped flank) at a dose of 0.5 ml per area per animal. The test material remained in contact with the skin for 24 h. Reactions were scored approximately 30 minutes after patch removal and 48 h later. The trade name mixture was classified as a non-irritant.

Anthemis Nobilis Flower Oil

Undiluted anthemis nobilis flower oil was applied to the backs of hairless mice (number and strain not stated). Details relating to the test procedure were not reported. The oil was classified as non-irritating.2 In another test, undiluted anthemis nobilis 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.2

Human

Predictive Testing

The skin irritation potential of anthemis nobilis 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.2

Skin Sensitization

Animal

Anthemis Nobilis Flower Oil

The skin sensitization potential of anthemis nobilis flower oil was evaluated in the open epicutaneous test on 6 guinea pigs (males and females).22 Using a pipette or syringe, anthemis nobilis flower oil (4% solution, 0.1 ml) was applied epicutaneously to an 8 cm² area of the clipped flank daily, and the test site remained uncovered for 24 h. These induction applications were repeated daily for 3 weeks. Reactions were scored either at the end of the application period or at the end of each week. The guinea pigs were challenged with the oil (on contralateral flank) on days 21 and 25. Ten guinea pigs served as controls. The anthemis nobilis flower oil solution was not allergenic in this study.

Human

Predictive Testing

Anthemis Nobilis Flower Oil

The skin sensitization potential of anthemis nobilis flower oil (4% in petrolatum) was evaluated in the maximization test using 25 healthy volunteers (21 to 44 years old).23 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.
Anthemis Nobilis Essential Oil

In a skin irritation and sensitization study, anthemis nobilis essential oil (concentration not stated) was initially applied to 113 healthy subjects (13 men, 100 women; 18 to 69 years old), 110 of whom completed the study. Three subjects withdrew for reasons unrelated to conduct of the study. The oil was applied, under an occlusive patch (volume and area not stated), between the scapulae of the upper back. Patches were applied to the same site on Mondays, Wednesdays, and Fridays for a total of nine 24-h induction applications. Removal of patches on Tuesdays and Thursdays was followed by a 24-h non-treatment period. Patch removal on Saturdays was followed by a 48-h non-treatment period. Reactions were scored during non-treatment periods. The challenge phase was initiated at the end of a 2-week non-treatment period. Challenge patches were applied to new test sites, and reactions were scored at 24 h, 48 h, 72 h, and 96 h post-application. At most, mild erythema was observed in 5 subjects during the induction phase. During the challenge phase, 1 subject had mild erythema and edema at the 48-h reading. This reaction had increased to well-defined erythema by the 72-h reading, but had diminished to mild erythema by the 96-h reading. During re-challenge of this subject (semi-occlusive, occlusive, and open patches used), barely perceptible erythema was observed at 24 h (occlusive patch test only). There were no visible skin reactions at 48 h or 72 h following application of any of the 3 types of patches. It was concluded that chamomile essential oil did not demonstrate a potential for eliciting dermal irritation or sensitization.

The skin irritation and sensitization potential of anthemis nobilis essential oil (concentration not stated) was evaluated in an RIPT that initially involved 122 healthy subjects (90 women, 32 men; 18 to 68 years old), 104 of whom completed the study. Eighteen subjects withdrew for reasons unrelated to conduct of the study, one of whom withdrew due to a generalized petechial response on most of the back. The oil (0.2 ml) was applied to a 2 cm x 2 cm semi-occlusive patch that was placed on the back (between the scapulae and waist, adjacent to the spinal midline) of each subject. The patches remained in place for 24 h. Removal of patches on Tuesdays and Thursdays was followed by a 24-h non-treatment period. Patch removal on Saturdays was followed by a 48-h non-treatment period. Reactions were scored during non-treatment periods. The test procedure was repeated on Mondays, Wednesdays, and Fridays for a total of 9 induction applications. The challenge phase was initiated at the end of a 2-week non-treatment period. Challenge patches were applied to new test sites, and reactions were scored at 24 h and 72 h post-application. Transient, barely perceptible erythema was observed in 8 of the 104 subjects during induction and/or challenge phases. These reactions were not classified as irritant or allergic in nature. It was concluded that chamomile essential oil did not induce skin irritation or allergenicity.

Provocative Testing

Anthemis Nobilis Extract

The sensitization potential of anthemis nobilis extract in patients sensitive to 5% Compositae mix (also contains anthemis nobilis extract) in petrolatum was evaluated using 76 patients. The extraction solvent was not stated. Anthemis nobilis extract (1% in petrolatum) was applied to the back of each of 29 patients (24 women [mean age = 56], 5 men [mean age = 55] 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. There were no positive reactions to anthemis nobilis extract.

Anthemis Nobilis

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 (0.5% in petrolatum) were patch tested with Anthemis nobilis (1% in petrolatum). 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 14 patients patch tested with Anthemis nobilis (1% in petrolatum), 6 had reactions that were described as follows: 2 with ++ reactions, 2 with doubtful positive follicular reactions, 1 with a + follicular reaction, and 1 with a doubtful positive reaction.

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. 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. 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.

**Anthemis Nobilis Flower**

Acute eczema on the forearms and hands was observed in a 50-year old metalworker after using a product for cleaning metallic items. 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) and, subsequently, with a tea made from chamomilla recutita (matricaria) (flower heads), anthemis nobilis (flower heads), and mallow herbs. Patch tests were performed using Finn chambers; neither the area of application nor test concentration was stated. Positive reactions to anthemis nobilis tea (++ on days 2 and 4) were reported. Negative results were reported for 5 control subjects tested with anthemis nobilis tea. 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.

**Anthemis Nobilis Flower Oil**

Severe exudative eczema of both nipples and areolae was observed in a 32-year-old woman who had been applying Kamillosan® ointment (containing extracts and oil of *Anthemis nobilis* 10.5%) to treat cracked nipples. It should be noted that 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*). Patch testing of the ointment (Finn chambers on Scanpor® tape) identified a 3+ reaction to the ointment at 2 days. A 3+ reaction was also observed after patch testing with 0.1% anthemis nobilis flower oil in petrolatum; results were negative in 10 control subjects. Bilateral eczema of the nipples and areolae was also observed in a 38-year-old woman who had used the same ointment. Patch testing also revealed a 3+ reaction to 0.1% anthemis nobilis flower oil in petrolatum at 2 days.

A 34-year-old woman with a history of atopic dermatitis was hospitalized with acute generalized eczema, accentuated on the face. Prior to the onset of symptoms, the patient had applied compresses of chamomile tea to her face and neck. Additionally, she drank chamomile tea regularly. Patch test results were as follows: 25% anthemis nobilis flower oil in olive oil (++ on day 2; +++ on day 3) and 4% anthemis nobilis flower oil in petrolatum (++ on day 2; +++ on day 3).

**Anthemis Nobilis and Anthemis Nobilis Extract**

A 55-year-old male employee of a magnet factory presented with crops of disseminated confluent erythroderma, initially on sun-exposed areas (face, neck, V of neck and acral) and then spreading to the remainder of the skin. The lesions were described as itchy and scaly. The patient experienced exacerbation of these reactions after visiting an area where there were many and varied plants, even though there was no direct contact with the plants. Patch testing with the *Anthemis nobilis* plant as is yielded a +++ reaction on days 2 and 4. The same reactions were reported after patch testing with *Anthemis nobilis* ethyl ether extracts (stem and leaves). Photopatch testing (Finn chambers, UVA exposure) also yielded a +++ reaction to the plant as is and its ethyl ether extracts.

**Phototoxicity**

**Anthemis Nobilis Flower Oil**

The phototoxicity of anthemis nobilis flower oil was evaluated using 12 Skh-1:hairless mice and 2 miniature swine. 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). The 12 mice and 2 swine were treated with the non-viscous oil, tested as received. A single application of the oil
(20 µl) was made to an area of the back that was approximately 2 cm². 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/m²), and 40 minutes (intensity of weighted erythemal energy = 0.1667 W/m²) 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, with appropriate vehicle only. Exposure to the xenon lamp caused barely perceptible erythema in animals pretreated with vehicle only or with anthemis nobilis flower oil. Parallel results were obtained using the blacklight lamp. 8-MOP was phototoxic.

**REPRODUCTIVE AND DEVELOPMENTAL TOXICITY**

**Chamomile**

A case-control analysis of data from the Quebec pregnancy registry was performed. Data on 3183 pregnant females were collected, and multivariate logistic regression models were used for data analysis.33 Cases were defined as women who delivered a newborn (< 2500 g), and 424 of the 3183 participants were classified as cases. After adjusting for potential confounders, there were no statistically significant associations found between the use of chamomile tea (alone or in combination with other herbal products) during the last 2 trimesters of pregnancy and the incidence of low birth weight.

An epidemiology study examined the use of herbal products by pregnant women in Italy and pregnancy outcome.34 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 hypothesized that the regular intake of 2 herbs (chamomile and licorice, taken from the beginning of pregnancy) may have had an influence on threatening miscarriages and preterm labors of low birth weight infants.

**GENOTOXICITY**

**Anthemis Nobilis Flower Oil**

The genotoxicity of anthemis nobilis flower oil was evaluated in the rec-assay using *Bacillus subtilis* strains PB 1652 and PB 1791 and in the *Salmonella*/microsome reversion assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537.35 In the rec-assay, 10-30 µl of the oil was applied to a sterile filter paper disk (9-mm diameter), placed on the surface of nutrient agar plates seeded with the tester strains. Following incubation, the diameter of the inhibition zones formed around the disk was measured. Methyl methanesulfonate (MMS), mitomycin C (MIT C), and adriamycin (ADR) served as positive controls. Ampicillin (AMP) and chloramphenicol (CAF) served as negative controls. Positive DNA-damaging activity was assumed if the ratio between the diameter of the inhibition zone of the rec’ mutant and that of the parental rec+ strain exceeded a value of 1.2. Anthemis nobilis flower oil did not produce positive DNA-damaging activity in either *Bacillus subtilis* strain. All positive controls had positive DNA damaging activity, whereas, the 2 negative controls did not. In the *Salmonella*/microsome reversion assay (with and without metabolic activation), the oil (in DMSO) was evaluated at doses up to 1 µl/plate and was not found to be genotoxic.

**CARCINOGENICITY**

Carcinogenicity studies on the *Anthemis nobilis*-derived ingredients reviewed in this safety assessment were not found in the published literature, nor were unpublished studies provided.
BIOLOGICAL ACTIVITY

Anti-inflammatory Activity

Anthemis Nobilis Flower Oil

The anti-inflammatory activity of anthemis nobilis flower oil was evaluated using groups of 6 adult male Wistar rats. The oil from 2 varieties of Anthemis nobilis that have been cultivated in Italy under the names “white-headed” (WH) or “double-flowered roman chamomile” and “yellow-headed roman chamomile” (YH) was tested. The oil from each flower type was administered i.p. at a dose of 350 mg/kg, and the animals were then dosed orally (gavage) with 5 ml water. Of the 2 control groups, 1 was injected i.p. with normal saline (dose not stated), and the other with indomethacin (14 µmol/kg). The dosing of control animals i.p. was followed by oral dosing with water. At 30 minutes post-treatment, the right hind paw was injected with 0.1 ml of a 1% suspension of carrageenan in normal saline to induce phlogosis. Each oil caused a considerable anti-inflammatory effect, particularly by 3 h post-injection. The oils caused 22.8 to 38.7% inhibition of the carrageenan-induced increase in paw volume. Indomethacin caused 73.7% inhibition.

SUMMARY

The safety of Roman chamomile [Anthemis nobilis]) ingredients is reviewed in this safety 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 3 chamomile ingredients have been used in cosmetic products: anthemis nobilis flower extract, anthemis nobilis flower oil, and anthemis nobilis flower water. Of the 3 ingredients, the highest ingredient use concentration has been reported as 10% for anthemis nobilis flower water.

Anthemis nobilis flower oil is produced by the steam distillation of Anthemis nobilis flowers.

A UV spectral analysis indicated an absorption maximum of ~225 nm for anthemis nobilis flower oil.

Anthemis nobilis flower oil did not induce acute toxicity when administered orally to rats.

A trade name mixture associated with anthemis nobilis flower extract (propylene glycol (and) water (and) anthemis nobilis flower extract) was classified as a very slight ocular irritant in rabbits. The mixture contained 5%-9.9% anthemis nobilis flower extract and was tested as a 20% v/v solution in distilled water.

Anthemis nobilis flower oil was classified as non-irritating to the skin of hairless mice and irritating to the skin of rabbits. A trade name mixture associated with anthemis nobilis flower extract (propylene glycol (and) water (and) anthemis nobilis flower extract) was also non-irritating to the skin of rabbits. The mixture contained 5%-9.9% anthemis nobilis flower extract and was tested as a 20% v/v solution in distilled water.

Anthemis nobilis flower oil (4%) did not induce skin sensitization in guinea pigs. In a human predictive patch test, anthemis nobilis flower oil (4%) was not a skin irritant in subjects tested or skin sensitizer in a maximization test involving 25 subjects. In 2 other human repeated insult patch tests, anthemis nobilis essential oil did not induce skin irritation or sensitization in 110 and 104 subjects, respectively.

Results were negative in 29 patients patch-tested with anthemis nobilis extract (1% in petrolatum). Provocative patch test reactions to Anthemis nobilis (plant part(s) not specified; 1% in petrolatum) were described as ++ reactions (2 of 14 patients) and doubtful positive follicular reactions (2 patients). Positive reactions to Anthemis nobilis ingredients were also observed in a number of case reports.

Barely perceptible erythema was observed in hairless mice and miniature swine treated with anthemis nobilis flower oil in a phototoxicity study, and these results were classified as negative.

In a case-control study (424 cases), there were no statistically significant associations found between the use of chamomile tea (alone or in combination with other herbal products) during the last 2 trimesters of pregnancy and the risk of low birth weight. 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.
Anthemis nobilis flower oil was not genotoxic in the rec-assay (no positive DNA-damaging activity) or Ames test. Carcinogenicity data on chamomile ingredients were not found in the published literature.

The anti-inflammatory activity of anthemis nobilis flower oil has been demonstrated in rats dosed intraperitoneally.

**DISCUSSION**

Although there are data gaps in this report, the Panel concluded that the interrelationships between molecular structures and physicochemical and biological characteristics (i.e., structure-property relationships), in conjunction with their functions and concentrations in cosmetics, allow grouping these ingredients together and extending the available toxicological data to support the safety of each of the ingredients in the group.

As 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. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse effects. In the absence of composition data on all anthemis nobilis-derived ingredients, except anthemis nobilis flower oil, the Panel agreed that the available data provide a reasonable assumption relative to the composition of the remaining *Anthemis nobilis*-derived ingredients. The Panel expressed concern about pesticide residues and heavy metals that may be present in *Anthemis nobilis*-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 noted that the highest use concentration reported for *Anthemis nobilis*-derived ingredients reviewed in this safety assessment is 10% anthemis nobilis flower water. Because use at this concentration was reported only for a single skin cleansing product in a survey of ingredient use concentrations, the Panel agreed that use at a concentration of 10% is not representative of typical use concentrations. Thus, the Panel determined that the negative HRIPT data on a product containing 3% anthemis nobilis flower extract are sufficient, together with other skin irritation and sensitization data in this safety assessment, for evaluating the skin irritation and sensitization potential of *Anthemis nobilis*-derived ingredients over the range of reported use concentrations. Although mammalian genotoxicity and carcinogenicity data were not available, the negative bacterial genotoxicity data, the available chemical composition data on these botanical ingredients, and the low use concentrations suggest that systemic toxicity would not be likely if percutaneous absorption of any of the constituents were to occur.

The Panel discussed incidental inhalation exposure from aerosol and pump hair sprays and foot 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 data characterizing the potential for these ingredients to cause acute 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](http://www.cir-safety.org/cir-findings).

**CONCLUSION**

The CIR Expert Panel concluded that anthemis nobilis extract, anthemis nobilis flower oil, anthemis nobilis flower powder, and anthemis nobilis flower water are safe in the present practices of use and concentration, described in this safety assessment, in cosmetics, when formulated to be non-sensitizing.
Table 1. Definitions and functions of the ingredients in this safety assessment

<table>
<thead>
<tr>
<th>Ingredient, CAS No.</th>
<th>Definition</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthemis Nobilis-Extract</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anthemis Nobilis Flower Oil</strong> [8015-92-7]</td>
<td>Anthemis Nobilis Flower Oil is the volatile oil distilled from the dried flower heads of <em>Anthemis nobilis</em>.</td>
<td>Fragrance ingredients; skin-conditioning agents-miscellaneous</td>
</tr>
<tr>
<td><strong>Anthemis Nobilis Flower Powder</strong></td>
<td>Anthemis Nobilis Flower Powder is the powder obtained from the dried, ground flowers of <em>Anthemis nobilis</em>.</td>
<td>Skin-conditioning agents-miscellaneous</td>
</tr>
<tr>
<td><strong>Anthemis Nobilis Flower Water</strong></td>
<td>Anthemis Nobilis Flower Water is an aqueous solution of the steam distillates obtained from the flowers of <em>Anthemis nobilis</em>.</td>
<td>Fragrance ingredients; skin-conditioning agents-miscellaneous</td>
</tr>
</tbody>
</table>

Table 2. Chemical and Physical Properties

<table>
<thead>
<tr>
<th>Properties</th>
<th>Anthemis Nobilis Flower Oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form</td>
<td>Light blue or light green-blue liquid with strong, aromatic odor</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>Between 0.892 and 0.910</td>
</tr>
<tr>
<td>Refractive Index</td>
<td>Between 1.440 and 1.450 at 20°C</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in most fixed oils and almost completely soluble in mineral oil. Soluble in propylene glycol, but insoluble in glycerin</td>
</tr>
<tr>
<td>Acid value</td>
<td>Not more than 15.0</td>
</tr>
<tr>
<td>Ester value</td>
<td>Between 250 and 310</td>
</tr>
<tr>
<td>Saponification number</td>
<td></td>
</tr>
<tr>
<td>UV absorption maximum</td>
<td>~ 225 nm</td>
</tr>
</tbody>
</table>
**Table 3. Composition Data on *Anthemis Nobilis* Trade Name Materria**

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>INCI Name</th>
<th>Composition (%)</th>
<th>Extraction Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetol® roman chamomile LC 376 Hydro</td>
<td>Propylene glycol (and) water (and) Anthemis nobilis flower extract</td>
<td>&gt; 50 %, 25% to 50%, 5% to 9.9%</td>
<td>Propylene glycol and water</td>
</tr>
</tbody>
</table>

**Table 4. Composition of Anthemis Nobilis Plant and Components.**

<table>
<thead>
<tr>
<th>Data</th>
<th>Plant Part/Derivative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Components/Impurities</td>
<td>Anthemis Nobilis Flower Oil</td>
</tr>
<tr>
<td>Aluminum</td>
<td>27 ppm</td>
</tr>
<tr>
<td>Angelyl angelate</td>
<td>1 to 5%</td>
</tr>
<tr>
<td>Ascorbic Acid</td>
<td>267 ppm</td>
</tr>
<tr>
<td>Ash</td>
<td>62,000 ppm</td>
</tr>
<tr>
<td>Beta-carotene</td>
<td>2.2 ppm</td>
</tr>
<tr>
<td>2-n-Butylangelate + hexyl acetate</td>
<td>14.5 to 34.2%</td>
</tr>
<tr>
<td>Butyl methacrylate, iso-2-propenoic acid, 2-methyl:isobutyl ether</td>
<td>1 to 5%</td>
</tr>
<tr>
<td>Calcium</td>
<td>6,720 ppm</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td></td>
</tr>
<tr>
<td>Chromium</td>
<td>6 ppm</td>
</tr>
<tr>
<td>Cobalt</td>
<td>58 ppm</td>
</tr>
<tr>
<td>EO</td>
<td>6,000 to 17,500 ppm</td>
</tr>
<tr>
<td>Fat</td>
<td>39,000 ppm</td>
</tr>
<tr>
<td>Fiber</td>
<td>72,000 ppm</td>
</tr>
<tr>
<td>Iron</td>
<td>170 ppm</td>
</tr>
<tr>
<td>Isoamyl angelate</td>
<td>1 to 22.8%</td>
</tr>
<tr>
<td>Isoamyl tiglate</td>
<td>0.6 to 0.8%</td>
</tr>
<tr>
<td>Isobutyl angelate</td>
<td>30 to 35%</td>
</tr>
<tr>
<td>Isobutyl butyrate</td>
<td>0.6 to 1.5%</td>
</tr>
<tr>
<td>Isobutyl isobutyrate</td>
<td>5 to 10 %</td>
</tr>
<tr>
<td>Isobutyl isovalerate</td>
<td>3.5 to 3.8%</td>
</tr>
<tr>
<td>Magnesium</td>
<td>2,920 ppm</td>
</tr>
<tr>
<td>Manganese</td>
<td>52 ppm</td>
</tr>
<tr>
<td>Methallyl angelate</td>
<td>5 to 10%</td>
</tr>
<tr>
<td>2-Methylbutyl angelate</td>
<td>15 to 20%</td>
</tr>
<tr>
<td>2-Methylbutyl-2-methylbutyrate pentan-2-yl butyrate</td>
<td>7.3% to 9.2%</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>3,220 ppm</td>
</tr>
<tr>
<td>α-Pinene</td>
<td>1 to 5%</td>
</tr>
<tr>
<td>Pinocarveol</td>
<td>1 to 5%</td>
</tr>
<tr>
<td>Potassium</td>
<td>13,200 ppm</td>
</tr>
<tr>
<td>Propyl angelate</td>
<td>1 to 5%</td>
</tr>
</tbody>
</table>
### Table 4. Composition of Anthemis Nobilis Plant and Components

<table>
<thead>
<tr>
<th>Components/Impurities</th>
<th>Anthemis Nobilis Flower Oil</th>
<th>Anthemis Nobilis Flower</th>
<th>Anthemis Nobilis Plant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>115,000 ppm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riboflavin</td>
<td>4.3 ppm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silicon</td>
<td>31 ppm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>2,580 ppm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamin</td>
<td>0.8 ppm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tin</td>
<td>10 ppm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>812,000 ppm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 5. Current Frequency and Concentration of Use According to Duration and Type of Exposure Provided in 2013

<table>
<thead>
<tr>
<th>Exposure Type</th>
<th>Anthemis Nobilis Flower Oil</th>
<th>Anthemis Nobilis Flower Water</th>
<th>Anthemis Nobilis Flower Extract</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># of Uses</td>
<td>Conc. (%)</td>
<td># of Uses</td>
</tr>
<tr>
<td><strong>Eye Area</strong></td>
<td>0.000057-</td>
<td>0.01</td>
<td>1</td>
</tr>
<tr>
<td>Incidental Ingestion</td>
<td>NR</td>
<td>2.8</td>
<td>NR</td>
</tr>
<tr>
<td>Incident Inhalation- Sprays</td>
<td>NR</td>
<td>2.8</td>
<td>NR</td>
</tr>
<tr>
<td>Incident Inhalation- Powders</td>
<td>2</td>
<td>0.00039-</td>
<td>2</td>
</tr>
<tr>
<td>Dermal Contact</td>
<td>6</td>
<td>2.8</td>
<td>1-10</td>
</tr>
<tr>
<td>Deodorant (underarm)</td>
<td>NR</td>
<td>0.00039-</td>
<td>NR</td>
</tr>
<tr>
<td>Hair - Non-Coloring</td>
<td>1</td>
<td>0.01</td>
<td>NR</td>
</tr>
<tr>
<td>Hair-Coloring</td>
<td>NR</td>
<td>0.00077-</td>
<td>NR</td>
</tr>
<tr>
<td>Nail</td>
<td>NR</td>
<td>2</td>
<td>NR</td>
</tr>
<tr>
<td>Mucous Membrane</td>
<td>NR</td>
<td>0.00039-</td>
<td>NR</td>
</tr>
<tr>
<td>Baby Products</td>
<td>3</td>
<td>0.007</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Duration of Use**

<table>
<thead>
<tr>
<th></th>
<th># of Uses</th>
<th>Conc. (%)</th>
<th># of Uses</th>
<th>Conc. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leave-On</td>
<td>0.00039-</td>
<td>2.8</td>
<td>2</td>
<td>1-4</td>
</tr>
<tr>
<td>Rinse off</td>
<td>2</td>
<td>0.05</td>
<td>NR</td>
<td>2-10</td>
</tr>
<tr>
<td>Diluted for (bath) Use</td>
<td>2</td>
<td>0.007</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Totals/Conc. Range**

|                                    | 0.000039- | 2.8 | 2 | 1-10 | 423 | 0.1 |

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.
References


19. McGeorge, B. C. and Steele, M. C. Allergic contact dermatitis of the nipple from Roman chamomile ointment. *Contact Dermatitis*. 1991;24(2):139-140.


