Final Report on the Safety Assessment of Yarrow (Achillea Millefolium) Extract[1]

Yarrow (Achillea Millefolium) Extract is an extract of the yarrow plant, *Achillea millefolium*, supplied in polypropylene glycol, which is reported to function as a "biological additive" in cosmetic products. Sesquiterpene lactones, polyacetylenes, simple coumarins, and flavonoids have been identified among the many components of *A. millefolium*. Yarrow Extract was reportedly used in 65 cosmetic formulations. Historically, Yarrow (Achillea Millefolium) Extract was reported to be used at concentrations of ≤25%, but recent data indicate that this ingredient is supplied with actual Yarrow (Achillea Millefolium) Extract content of 2% to 25% and used at concentrations of 0.5% to 10%. Only limited toxicity data were available. Guinea pigs were sensitized to crude extracts of the whole plant and the flowers of *A. millefolium*. *A. millefolium* tea was weakly genotoxic in a somatic mutation and recombination test using *Drosophila melanogaster*. In clinical testing, product formulations containing 0.1% to 0.5% of ingredient that actually contained 2% of Yarrow Extract were generally not irritating. In provocative testing, patients reacted to a *Compositae* mix that contained yarrow, as well as to yarrow itself. Also in clinical testing, a formulation containing 0.1% Yarrow (Achillea Millefolium) Extract (2% Yarrow in propylene glycol and water) was not a sensitizer in a maximization test and alcoholic extracts of dried leaves and stalks of *A. millefolium* did not produce a phototoxic response. These data were not considered sufficient to support the safety of this ingredient in cosmetics. The types of data (all testing is to be performed on cosmetic-grade ingredients) still required include (1) ultraviolet (UV) absorption data, if absorption occurs in the UVA or UVB range, photosensitization data are needed; (2) gross pathology and histopathology in skin and other major organ systems associated with repeated exposures; (3) reproductive and developmental toxicity data; (4) two genotoxicity studies, one using a mammalian system, if positive, a 2-year dermal carcinogenicity assay performed using National Toxicology Program (NTP) methods may be needed; and (5) clinical sensitization testing at maximum concentration of use. In the absence of these data, it was concluded that the available data are insufficient to support the safety of Yarrow (Achillea Millefolium) Extract for use in cosmetic products.

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INTRODUCTION

The safety of Yarrow (Achillea Millefolium) Extract as used in cosmetic formulations is reviewed in this report. Yarrow (Achillea Millefolium) Extract is obtained from the yarrow plant *Achillea millefolium*, supplied in polypropylene glycol, and is described as a "biological additive" in cosmetic formulations (Wenninger and McEwen 1997).

CHEMISTRY

Definition and Structure

Yarrow (Achillea Millefolium) Extract (CAS No. 84082-83-7) is an extract of the yarrow *A. millefolium* (Wenninger and McEwen 1997). It is also known as Yarrow Extract; Extract of Yarrow; Achillea Millefolium Extract; Extract of Achillea Millefolium; and Milfoil Extract (Wenninger and McEwen 1997). *A. millefolium* L. is also known as milfoil, nosebleed, thousand leaf (Leung and Foster 1996), knight's milfoil, soldier's woundwort, and military herb (Hausen et al. 1991).

Physical and Chemical Properties

Yarrow (Achillea Millefolium) Extract (as 10% to 25% Yarrow (Achillea Millefolium) Extract and >75% propylene glycol) is a clear, brownish-green liquid with a faint herbal odor (Grau Aromatics GmbH & Co. 1997). It is soluble in water, has a refractive index of 1.430 to 1.440 (at 20°C), density of 1.030 to 1.050 (at 20°C), and a pH value of 5.5 to 6.5.

Manufacture and Production

A glycolic extract using the flowers of *A. millefolium* was prepared by percolation with propylene glycol under vacuum to final E/D ratio of 2:1 (Council of Europe 1989).

Yarrow (Achillea Millefolium) Extract (as 10% to 25% Yarrow (Achillea Millefolium) Extract and >75% propylene glycol) is prepared by extracting yarrow flowers with 1,2-propylene glycol; the ratio of extract to botanical is 5:1 (Grau Aromatics GmbH & Co. 1997). Two preservatives, phenonip (phenoxyethanol plus methylparaben, butylparaben, ethylparaben, and propylparaben), 0.4%, and imidazolidinyl urea, 0.2%, are used. Another supplier stated that Yarrow (Achillea Millefolium) Extract is manufactured by extraction in solvent medium (Provital S.A. 1998). The component breakdown of

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Yarrow (Achillea Millefolium) Extract is 2% to 5% Yarrow (Achillea Millefolium) Extract, 70% to 90% propylene glycol, 10% to 30% water, and 0.5% phenonip. A third company reported that air dried Yarrow (Achillea Millefolium) Extract usually undergoes a "cold" (40°–50°C) extraction process with a mixture of ethyl alcohol and water that occurs over a 48-hour period and includes several washes of the solvent mixture (Madis Botanicals 1998). The hydroalcoholic extract is filtered and concentrated under vacuum to a viscous liquid with approximately 50% to 60% solids. The supplier states that the concentrate is then diluted with "customer specified solvents such as propylene or butylene glycol." The use of propylene or butylene glycol results in "glycolic extract" finished products; products that use combinations of water and glycols produce "hydroglycolic extracts." Use of a heated oil extraction process results in a "liposoluble extract."

Analytical Methods

Column chromatography, analytical and preparative thin-layer chromatography, and various spectroscopic techniques were used to isolate and identify sesquiterpene lactones of *A. millefolium* (Hausen et al. 1991). Column chromatography was used to separate and identify flavonoids of the flowering heads of *A. millefolium* L., and spectral studies, that is, paramagnetic resonance (PMR) (not identified), mass spectrometry, and ultraviolet (UV), were used to establish the substances found (Falk et al. 1975).

Composition

Ten sesquiterpene lactones and three polyacetylenes have been identified in *A. millefolium* (Hausen et al. 1991). *A. millefolium* also contains simple coumarins (Council of Europe 1989) and flavonoids (Falk et al. 1975). The flowering heads contain 5-hydroxy-3,6,7,4′-tetramethoxyflavone, artemetin, and casticin. The flavonoids apigenin, luteolin-7-glycosides, caffeic acid, and isorhamnetin have also been identified as constituents of the plant. Yarrow contains 0.2 to ~1% of essential oil, which, depending on the origin, can contain 0% to 50% chamazulene (Bisset 1994). A correlation exists between the presence of prochamazulene and the chromosome number; only tetraploid plants contain azulene. The main components of oil that did not contain azulene were camphor (18%), sabinene (12%), 1,8-cineole (10%), α-pinene (9%), and isoartemisia ketone (9%). In azulene-containing oil, chamazulene (25%), β-pinene (23%), caryophyllene (10%), and α-pinene (5%) were the main components, along with achillicin, (a proazulene), several sesquiterpene lactones, several flavonoids, phenolic acids, triterpenes and sterols, *N*-containing compounds, coumarins, and tannins. Yarrow also contains a trace of thujone (Leung and Foster 1996).

A supplier of Yarrow (Achillea Millefolium) Extract (as 10% to 25% Yarrow (Achillea Millefolium) Extract and >75% propylene glycol) stated that it contains acetylene compounds, sesquiterpene lactone, succininic and salicylic acids, cyanogenetic heteroside, fatty acids, amino acids, flavonoids, essential oil, alkanes, coumarins, tannins, sugars, polyalcohols, phenol acids, vitamin C, mucilages, resins, phytosterols, and alkaloids (Grau Aromatics GmbH & Co. 1997).

Impurities

Yarrow (Achillea Millefolium) Extract (as 10% to 25% Yarrow (Achillea Millefolium) Extract and >75% propylene glycol) contains ≤1 ppm heavy metals (Grau Aromatics GmbH & Co. 1997). Another supplier stated that Yarrow (Achillea Millefolium) Extract (as 2% Yarrow (Achillea Millefolium) Extract with propylene glycol and water) contains <20 ppm heavy metals as Pb (Provital S. A. 1998). No data were available as to the presence of pesticides, but none were expected to be found. Evaluation for 1,4-dioxane, ethylene oxide, solvent residues (benzene, etc.), monomers, free amines, nitrosamines, and polycyclic aromatic hydrocarbons was not applicable. Thujone was not detected in yarrow volatile oil (Bio-Botanica, Inc. 1998).

Two preservatives, phenonip, 0.4%, and imidazolidinyl urea, 0.2%, are used in the manufacture and production of Yarrow (Achillea Millefolium) Extract.

Ultraviolet Absorbance

Published data on the UV absorbance of Yarrow (Achillea Millefolium) Extract were not found.

USE

Cosmetic

Yarrow (Achillea Millefolium) Extract is described as a "biological additive" in cosmetics (Wenninger and McEwen 1997). The product formulation data submitted to the FDA in 1998 indicated that Yarrow (Achillea Millefolium) Extract was used in a total of 65 cosmetic product formulations (FDA 1998) (Table 1).

Concentration of use values are no longer reported to the FDA by the cosmetic industry (FDA 1992). One manufacturer reported that Yarrow (Achillea Millefolium) Extract is used in shampoos at a concentration of 0.5% (Cosmetic, Toiletry, and Fragrance Association [CTFA] 1998), another supplier reported that Yarrow (Achillea Millefolium) Extract (as 10% to 25% Yarrow Extract and >75% propylene glycol) is used at 1% to 10% in cosmetic products (Grau Aromatics, GmbH & Co. 1997), a third supplier stated that the suggested concentration of use of Yarrow (Achillea Millefolium) Extract (containing 2% to 5% Yarrow (Achillea Millefolium) Extract with propylene glycol and water) is 1% to 3%, with a maximum concentration of use of 5% (Provital S.A. 1998), and a fourth supplier stated that the percentage of Yarrow (Achillea Millefolium) Extract in finished formulations ranges from 0.5% to 5% (Madis Botanicals 1998). The product formulation data submitted to the FDA in 1984 stated that Yarrow (Achillea Millefolium) Extract (as Yarrow Extract) was used at concentrations of ≤25% (Table 2).

TABLE 1
Product formulation data (FDA 1998)

Product category	Total no. of formulations in category	Total no. containing ingredient
Bubble bath	200	1
Other eye makeup preparations	120	1
Hair conditioners	636	4
Rinses (noncoloring)	40	1
Shampoos (noncoloring)	860	9
Tonics, dressings, and other hair-grooming aids	546	10
Wave sets	55	1
Bath soaps and detergents	385	1
Deodorants (underarm)	250	1
Other shaving preparation products	60	1
Cleansing preparations	653	5
Depilatories	28	1
Face and neck preparations (excluding shaving)	263	2
Body and hand preparations (excluding shaving)	796	5
Moisturizing preparations	769	3
Paste masks (mud packs)	255	2
Skin fresheners	184	6
Other skin care preparations	692	7
1998 total		**61**
Tradename uses		
No. of uses as part of a tradename mixture		4

International

Yarrow (Achillea Millefolium) Extract, as Yarrow Extract, is listed in the *Japanese Comprehensive Licensing Standards of Cosmetics by Category (CLS)* (Rempe and Santucci 1997). Yarrow Extract which conforms to the specifications of the *Japanese Cosmetic Ingredients Codex* has precedent for use without restriction in all *CLS* categories.

Yarrow (Achillea Millefolium) Extract does not appear in Annex II (list of substances which must not form part of the composition of cosmetic products) or Annex III (list of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down) of the Cosmetics Directive of the European Union (European Economic Community 1995). The Council of Europe Committee of Experts has classified botanicals according to safety (Patri and Silano 1994). Yarrow was classified in group 3, which is the grouping for "recommended ingredients" which can be "safely used in cosmetic products for the purposes stated according to reported use levels."

Noncosmetic Use

Yarrow (*A. millefolium* L.) is cleared for use in beverages, providing the finished beverage is thujone free, when used in the minimum quantity to produce the intended effect and in accordance with good manufacturing practice (FDA 1997). Thujone, a ketone derived from thujane, may cause convulsions and hallucinations if ingested (Bio-Botanica, Inc. 1998). Yarrow is used in folk medicine in combination with other botanicals for treating colds and flu (Hausen et al. 1991).

GENERAL BIOLOGY

Published data on Yarrow (Achillea Millefolium) Extract normally included in this section were not found.

ANIMAL TOXICOLOGY

The oral and subcutaneous LD_{50} values of Yarrow (Achillea Millefolium) Extract (2% Yarrow in propylene glycol and water) are both 1 g/kg for the mouse (Provital S.A. 1998).

Dermal Irritation

Published data on the dermal irritation of Yarrow (Achillea Millefolium) Extract were not found.

Sensitization

Groups of 10 guinea pigs were used to determine the sensitization potential, via a modified Freund's complete adjuvant method, of 0.1% and 1% *A. millefolium* as a crude extract of the whole plant, and groups of 3 guinea pigs were used to determine the sensitization potential of 0.1% and 1% *A. millefolium* as a crude extract of the flowers (Hausen et al. 1991). The sensitization potential of the sesquiterpene lactone α-peroxyachifolid was also tested at 0.01% and 0.1% using groups of 10 guinea pigs and at 1% using a group of 3 guinea pigs. All animals tested with extracts of the whole plant were sensitized. Animals tested with the flower extract were challenged with either the flower extract or α-peroxyachifolid; all animals tested with the flower extract were sensitized. The groups of 10 guinea pigs tested with 0.01% or 0.1% α-peroxyachifolid were challenged with the lactone and the 3 animals tested with 1% α-peroxyachifolid were challenged with the flower extract; all animals tested with the lactone were sensitized. Groups of three animals that were induced with the flower extract and sensitized with other lactones (dehydroxymatricaria ester, pontica epoxide, artemisia ketone, and β-peroxyisoachifolid) were not sensitized.

Ocular Irritation

Published data on the ocular irritation of Yarrow (Achillea Millefolium) Extract were not found.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Published data on the reproductive and developmental toxicity of Yarrow (Achillea Millefolium) Extract were not found.

TABLE 2
Concentration of use data (FDA 1984)

Product category	10%–25%	1%–5%	0.1%–1%	0%–0.1%	Unknown	Total
Bubble baths					1	1
Hair conditioners				3	2	5
Permanent waves				2	2	4
Shampoos (non-coloring)				9	12	21
Wave sets				1		1
Other hair preparations					1	1
Other hair-coloring preparations					1	1
Face powders				1		1
Skin cleansing products (cold creams/lotions/liquids/pads)				1	4	5
Face/body/hand preparations (excluding shaving preparations)	1		2	1	8	12
Moisturizing products				1	1	2
Night preparations				1	1	2
Paste masks (mud packs)					2	2
Skin fresheners		1		2	6	9
Other skin care preparations			1		7	8
Other suntan preparations					1	1
Total	1	1	3	22	49	76

GENOTOXICITY

A somatic mutation and recombination test using *Drosophila melanogaster* was performed to determine the genotoxic potential of 20% and 40% *A. millefolium* herbal tea extract (Graf et al. 1994). The *A. millefolium* tea was weakly genotoxic; the effect could have been due to the presence of flavonoids.

Saigusa et al. (1987) reported that *A. millefolium* L. inhibited induction of mutations by UV, 4NQO, AF-2, MMS, EMS, MNNG, and ENNG (compounds not identified). The effect on UV survivals of *Escherichia coli* strains WP2uvrA and CM571 was examined. *A. millefolium* increased UV survival of WP2uvrA but not CM571. (Other details not reported.)

CARCINOGENICITY

Published data on the carcinogenic potential of Yarrow (Achillea Millefolium) Extract were not found.

CLINICAL ASSESSMENT OF SAFETY

Irritation

Predictive Testing

A single-insult occlusive patch test was performed using 20 subjects with a shampoo formulation containing 0.5% Yarrow (Achillea Millefolium) Extract (2% extract) (CTFA 1991a). The formulation had a primary irritation index (PII) of 0.25; no significant difference in irritancy was observed between the test and control formulations.

Three 4-day minicumulative patch tests were performed with face cream formulations containing 0.1% Yarrow (Achillea Millefolium) Extract (2% extract). In the first study (CTFA 1991b), two formulations, both pH 4.45, were applied under occlusive patches and had PIIs of 0.39 and 0.24. Both had "acceptable irritancy results." In the second study (CTFA 1993a), the formulation had a PII of 0.55. Fourteen subjects (total number of subjects not specified) reacted and five had follicular-type responses. One subject, who did not react to the vehicle, had a "very strong response" to the test formulation, and overall the test formulation was "significantly more irritating than the vehicle." In the third assay (CTFA, 1993b), which involved four consecutive 24-hour patches to the same site followed by grading 5 hours after removal of the final patch, the formulation had a PII of 0.38.

Three- and 4-week split-face clinical use tests were performed with face cream formulations containing 0.1% Yarrow (Achillea Millefolium) Extract (2% extract). In the 3-week study (CTFA 1991c), 26 "regular moisturizer users" applied the test and a control product twice daily with no product cross-over. No irritation was observed. One and two subjects reported discomfort with the test and control products, respectively. In the 4-week study (CTFA 1993c), 33 "moisturizer users" applied the test formulation and a control formulation, which was a modified in-line cream. The test and control formulations produced similar visible irritation, 36% and 39%, respectively. Two subjects reported discomfort to the test and control formulations.

A patch test was performed according to the methods of the International Contact Dermatitis Research Group (ICDRG) with

the European standard series and some Compositae allergens, including 1% *A. millefolium* in petrolatum, using 16 subjects (Wrangsjö, Ros, and Wahlberg 1990). The Compositae allergens were applied for 24 hours, and the test sites were scored after 20 and 60 minutes and 48 and 96 hours. *A. millefolium* as the plant extract produced positive results for 4 of the 16 subjects. Using the pollen "as is," a positive result was produced in 1 of 15 subjects. The flower of *A. millefolium* was tested "as is," either fresh or deep frozen for 6 months, and it produced a positive reaction in the one patient tested.

Provocative Testing

A *Compositae* mix consisting of a short ether extract of 1.0% *A. millefolium* L. and other species was included in a standard series and patch tested on 3851 patients over a 5-year period (Hausen 1996). The mix was applied to the back of each patient for 24 hours using Finn chambers, and the sites were scored according to the ICDRG. If a positive reaction was observed, extracts of the individual species were tested 1 week later. One hundred eighteen patients (3.1%), 44 males and 74 females, had a positive reaction to the mix; it was determined that 33 of these patients acquired this hypersensitivity occupationally. Of 85 patients tested with the individual species, 45 (53%), 19 males and 26 females, reacted to *A. millefolium* L.

Of 3489 patients tested over 5 years with a *Compositae* mix that contained 1% yarrow, 124 had a positive reaction (Hausen et al. 1991). Of 83 patients with plant dermatitis tested with individual *Compositae* mix components, 47 had a positive reaction to yarrow (ranging from + to +++).

Sensitization

The sensitization potential of a face cream formulation containing 0.1% Yarrow (Achillea Millefolium) Extract (2% extract) was determined in a maximization test completed with 25 subjects (Ivy Laboratories 1991). The formulation was not irritating in a pretest in which 0.1 g was applied under an occlusive patch for 48 hour; therefore the test sites were pretreated with sodium lauryl sulfate (SLS) prior to test material application during induction and challenge. During induction, 0.1 ml of 1% aqueous SLS was applied under an occlusive patch to the test site on the upper outer arm of each subject. After 24 hours, the SLS patch was removed and an occlusive patch containing 0.1 g of the test material was applied for 48 to 72 hours; the patch was then removed and the site was examined for irritation. If irritation was not observed, SLS pretreatment was used with the next application; this sequence was continued for a total of five induction exposures. After a 10-day nontreatment period, an occlusive patch containing the test material was applied to a previously unexposed site on the opposite arm for 48 hours; the challenge site was pretreated for 1 hour with 0.1% of 10% aqueous SLS under an occlusive patch. The challenge site was graded 1 and 24 hours after patch removal. The formulation containing 0.1% Yarrow (Achillea Millefolium) Extract (2% extract) was not a sensitizer.

Phototoxicity

The phototoxicity potential of alcoholic extracts of dried leaves and stalks of *A. millefolium* (presumed to be 1% in alcohol [96%]) was determined (Van Dijk and Berrens 1964). A 1 × 2-cm area of the upper arm of a test subject (number of subjects not stated) was moistened with the extract, and the site was covered after the solvent evaporated. After 1.5 hours, the test area was irradiated for 5 minutes using an apparatus (described by Rottier and Van der Leun 1960) that had as its light source "a water-cooled super high-pressure mercury lamp (SP 500, Philips)." Monochromatic light (366 mμ), obtained using an interference filter, was used. *A. millefolium* did not produce a phototoxic response.

SUMMARY

Yarrow (Achillea Millefolium) Extract is an extract of the yarrow, *A. millefolium*, and functions as a biological additive in cosmetic products. Sesquiterpene lactones, polyacetylenes, and flavonoids have been identified as components of *A. millefolium*, and chamazulene can exist in the essential oil. In 1998, it was reported to the FDA that Yarrow (Achillea Millefolium) Extract was used in 65 cosmetic formulations. In 1984, Yarrow Extract was reported to be used at concentrations of ≤25%. Submissions from suppliers indicate that Yarrow (Achillea Millefolium) Extract (actual Yarrow Extract content of 2% to 25%) is used at concentrations of 0.5% to 10%.

The oral and subcutaneous LD_{50} of Yarrow (Achillea Millefolium) Extract were both 1 g/kg for the mouse. Guinea pigs were sensitized to crude extracts of the whole plant and the flowers of *A. millefolium*. *A. millefolium* tea was weakly genotoxic in a somatic mutation and recombination test using *Drosophila melanogaster*. In clinical testing, product formulations containing 0.1% to 0.5% Yarrow (Achillea Millefolium) Extract (2% extract) were generally not irritating. In provocative testing, a number of patients reacted to a Compositae mix that contained yarrow, as well as to yarrow itself. Also in clinical testing, a formulation con-taining 0.1% Yarrow (Achillea Millefolium) Extract (2% Yarrow in propylene glycol and water) was not a sensitizer and alcoholic extracts of dried leaves and stalks of *A. millefolium* did not produce a sensitization response.

DISCUSSION

Section 1, paragraph (p), of the Cosmetic Ingredient Review (CIR) Procedures states that "A lack of information about an ingredient shall not be enough to justify a determination of safety." In accordance with Section 30(j)(2)(A) of the Procedures, the Expert Panel informed the public of its decision that the data on Yarrow (Achillea Millefolium) Extract were insufficient to determine whether Yarrow (Achillea Millefolium) Extract was either safe or unsafe. The Expert Panel released a Notice of Insufficient Data Announcement on September 23, 1997, outlining the data needed to assess the safety of Yarrow (Achillea Millefolium) Extract. Data on irritation and sensitization,

chemical characterization, method of manufacture, impurities, and current concentration of use were received. The types of data still required include[2]

1. UV absorption data; if absorption occurs in the UVA or UVB range, photosensitization data are needed.
2. Gross pathology and histopathology in skin and other major organ systems associated with repeated exposures.[3]
3. Reproductive/developmental toxicity data.[3]
4. Two genotoxicity studies, one using a mammalian system; if positive, a 2-year dermal carcinogenicity assay performed using National Toxicology Program (NTP) methods may be needed.
5. Clinical sensitization testing (repeated-insult patch test with 150 subjects) at maximum concentration of use.

No offer to supply these remaining data was received. In accordance with Section 45 of the CIR Procedures, the Expert Panel has issued a Final Report—Insufficient Data. When the requested data are available, the Expert Panel will reconsider the Final Report in accordance with Section 46 of the CIR Procedures, Amendment of a Final Report.

CONCLUSION

The CIR Expert Panel concludes that the available data are insufficient to support the safety of Yarrow (Achillea Millefolium) Extract for use in cosmetic products.

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[2]All testing is to be performed on cosmetic-grade ingredients.

[3]These are data that would be expected from what is commonly referred to as a "28-day dermal toxicity study."

[4]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.