Final Report on the Safety Assessment of Calendula Officinalis Extract and Calendula Officinalis[1]

Calendula Officinalis Extract is an extract of the flowers of *Calendula officinalis*, the common marigold, whereas Calendula Officinalis is described as plant material derived from the flowers of *C. officinalis*. Techniques for preparing Calendula Officinalis Extract include gentle disintegration in soybean oil. Propylene glycol and butylene glycol extractions were also reported. Components of these ingredients are variously reported to include sugars, carotenoids, phenolic acids, sterols, saponins, flavonoids, resins, sterins, quinones, mucilages, vitamins, polyprenylquinones, and essential oils. Calendula Officinalis Extract is reported to be used in almost 200 cosmetic formulations, over a wide range of product categories. There are no reported uses of Calendula Officinalis. Acute toxicity studies in rats and mice indicate that the extract is relatively nontoxic. Animal tests showed at most minimal skin irritation, and no sensitization or phototoxicity. Minimal ocular irritation was seen with one formulation and no irritation with others. Six saponins isolated from *C. officinalis* flowers were not mutagenic in an Ames test, and a tea derived from *C. officinalis* was not genotoxic in *Drosophila melanogaster*. No carcinogenicity or reproductive and developmental toxicity data were available. Clinical testing of cosmetic formulations containing the extract elicited little irritation or sensitization. Absent any basis for concluding that data on one member of a botanical ingredient group can be extrapolated to another in a group, or to the same ingredient extracted differently, these data were not considered sufficient to assess the safety of these ingredients. Additional data needs include current concentration of use data; function in cosmetics; ultraviolet (UV) absorption data; if absorption occurs in the UVA or UVB range, photosensitization data are needed; gross pathology and histopathology in skin and other major organ systems associated with repeated dermal exposures; dermal reproductive/developmental toxicity data; inhalation toxicity data, especially addressing the concentration, amount delivered, and particle size; and genotoxicity testing in a mammalian system; if positive, a 2-year dermal carcinogenicity assay performed using National Toxicology Program (NTP) methods is needed. Until these data are available, it is concluded that the available data are insufficient to support the safety of these ingredients in cosmetic formulations.

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. Monice Zondlo Fiume, former Scientific Analyst/Report Management Coordinator, prepared this report. Address correspondence to Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

INTRODUCTION

The safety of Calendula Officinalis Extract and Calendula Officinalis used in almost 200 cosmetic formulations, ranging from skin and eye cosmetics through hair products and soaps, is reviewed in this report. Both Calendula Officinalis Extract and Calendula Officinalis are obtained from the calendula, *Calendula officinalis*, and serve as biological additives (Wenninger and McEwen 1997).

CHEMISTRY

Definition

Calendula Officinalis Extract (CAS No. 84776-23-8) is an extract of the flowers of the calendula, *C. officinalis* (Wenninger and McEwen 1997). It is also known as Calendula Extract; Extract of Calendula; Extract of Calendula Officinalis; and Marigold Extract.

Calendula Officinalis is a plant material derived from the flowers of *C. officinalis* (Wenninger and McEwen 1997). It is also known as Calendula and Calendula Powder. The plant Calendula is also known as marigold, garden marigold, pot marigold, Marybud, holigold (Fleischner 1985), holligold, and gold-bloom (Budavari 1989).

Physical and Chemical Properties

A mixture of Calendula Officinalis Extract (1%–5%), soybean (Glycine Soja) oil (>50%), and tocopherol (<0.1%) is a reddish-yellow oily liquid with an aromatic herbal odor (Chemisches Laboratorium Dr. Kurt Richter GmbH 1996). It is soluble in fats and oils, has a refractive index (n_D20°C) of 1.474 to 1.475, density of 0.918 to 0.922 g/ml, and an acid value of <1.0. A mixture of Calendula Officinalis Extract (10%–25%) and propylene glycol (>75%) is a clear, brown liquid with a faint herbal odor (Grau Aromatics GmbH & Co. 1998). It is soluble in water, has a refractive index of 1.425 to 1.445 (at 20°C), density of 1.035 to 1.055 (at 20°C), and a pH value of 5.5 to 6.5. A mixture of Calendula Officinalis Extract, butylene glycol, and water (percentages not specified) is a yellowish-brown, transparent liquid with a bitter taste (Ichimaru Pharcos Co., Ltd. 1994). It has a specific gravity (d20/20) of 1.01 to 1.05 and a pH of 5.0 to 6.0.

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Manufacture and Production

A mixture containing Calendula Officinalis Extract (1%–5%), soybean (Glycine Soja) oil (>50%), and tocopherol (<0.1%) is characterized as a fatty oil extract of calendula blossoms; the fatty oil used is soybean oil (Chemisches Laboratorium Dr. Kurt Richter GmbH 1996). The calendula blossoms are "gently disintegrated and extracted with stabilized soybean oil." The mixture is then obtained by filtration.

A mixture of Calendula Officinalis Extract (10%–25%) and propylene glycol (>75%) is prepared by extracting calendula blossoms with 1,2-propylene glycol; the ratio of extract to botanical is 5:1 (Grau Aromatics GmbH & Co. 1998). A preservative, 0.6% phenonip (phenoxyethanol, methylparaben, butylparaben, ethylparaben, and propylparaben), is used.

A mixture of Calendula Officinalis Extract, butylene glycol, and water (percentages not specified) is prepared by extracting calendula flowers with 1,3-butylene glycol (Ichimaru Pharcos Co. Ltd. 1994).

Composition

The blossoms of *C. officinalis* contain carotenoid pigments, a saponin, a "bitter principle," and calendulin (Fleischner 1985). Vidal-Ollivier et al. (1990) reported that six saponins were determined in six cultural varieties of *C. officinalis*, and that the concentration of the saponin was dependent upon the variety and the date of harvest. Calendula is also composed of volatile oil, caledin (Budavari 1989), and flavonol-3-*O*-glycosides (Vidal-Ollivier et al. 1991; Pietta et al. 1992), and *C. officinalis* contains acylated steryl glucosides that are composed of C_{12}–C_{22} fatty acids (Wojciechowski and Zimowski 1975). Extract of *C. officinalis* in propylene glycol contained sugars, carotenoids, flavonoids, and essential oils components and an extract in isopropyl myristate contained carotenoids, phenolic acids, sterols, and essential oil components (Góra et al. 1980).

A supplier of a mixture containing Calendula Officinalis Extract and propylene glycol stated that the plant is composed of essential oil, carotenoids, flavonoids, triterpenic alcohols, organic acids and esters, sterins, quinones, mucilages, saponins, resins, vitamins, polyprenylquinones, and bitter substances (Grau Aromatics GmbH & Co. 1998). A supplier of a mixture containing Calendula Officinalis Extract and butylene glycol and water stated that the main elements of the plant are flavonoid, saponine, and amino acid (Ichimaru Pharcos Co., Ltd. 1994).

Analytical Methods

High-performance liquid chromatography (HPLC) (Vidal-Ollivier et al. 1991), reversed-phase HPLC, and micellular electrokinetic capillary chromatography have been used to analyze *C. officinalis* (Pietta et al. 1992). Fractionation by column chromatography and thin layer chromatography have been used to determine some terpene derivatives of *C. officinalis* (Gracza 1987).

A mixture of Calendula Officinalis Extract (1%–5%), soybean (Glycine Soja) oil (>50%), and tocopherol (<0.1%) is identified using the "total of quality control data" (Chemisches Laboratorium Dr. Kurt Richter GmbH 1996).

Ultraviolet Absorption

Published data on the ultraviolet absorption of Calendula Officinalis Extract and Calendula Officinalis were not found.

Impurities

A mixture of Calendula Officinalis Extract, butylene glycol, and water contains ≤10 ppm heavy metals and ≤1 ppm arsenic (Ichimaru Pharcos Co., Ltd. 1994).

USE

Cosmetic

Calendula Officinalis Extract and Calendula Officinalis are reported to function as biological additives (Wenninger and McEwen 1997). The product formulation data submitted to the Food and Drug Administration (FDA) in 1998 reported that Calendula Officinalis Extract was used in 178 cosmetic formulations, 177 used under the name Calendula Extract and 1 under the named Calendula Fluid Extract, and that Calendula Officinalis was not used (FDA 1998) (Table 1).

Concentration of use values are no longer reported to the FDA by the cosmetics industry (FDA 1992). Data submitted by the cosmetics industry reported that one company uses Calendula Officinalis Extract at concentrations of <0.5% in a styling gel, a shampoo, and a cream rinse; another company uses it at a concentration of 0.2 weight % (CTFA 1998); and a supplier states that a mixture of Calendula Officinalis Extract (10%–25%) and propylene glycol (>75%) is used at 1%–10% in cosmetic products (Grau Aromatics, GmbH & Co. 1998). Product formulation data submitted to the FDA in 1984 stated that Calendula Officinalis Extract was used in 24 cosmetic formulations, 12 at concentrations of ≤10% and 12 at unknown concentrations, and that Calendula Officinalis was used in 3 cosmetic formulations at concentrations of <5% (FDA 1984) (Table 2).

International

Calendula Officinalis Extract and Calendula Officinalis, as Calendula Extract, are listed in the *Japanese Comprehensive Licensing Standards of Cosmetics by Category (CLS)* (Rempe and Santucci 1997). Calendula Extract which conforms to the specifications of the *Japanese Cosmetic Ingredients Codex* (*JCIC*) has precedent for use without restriction in all *CLS* categories. Calendula Officinalis, as Calendula Powder, is also listed in the *CLS*. Calendula Powder, which conforms to the specifications of the *JCIC*, has precedent for use in all *CLS* categories without restriction except eyeliner, lip, and oral preparations, for which there is no precedent for use.

TABLE 1
Calendula Extracts product formulation data (FDA 1998)

Product category	Total no. of formulations in category	Total no. containing ingredient
Baby lotions, oils, powders, and creams	53	3
Other baby products	29	1
Bath oils, tablets, and salts	124	2
Bubble baths	200	1
Other bath preparations	159	1
Eyeliner	514	1
Eye shadow	506	1
Eye lotion	18	2
Other eye makeup preparations	120	5
Other fragrance preparations	148	2
Hair conditioners	636	9
Hair sprays (aerosol fixatives)	261	1
Hair straighteners	63	1
Permanent waves	192	4
Rinses (noncoloring)	40	3
Shampoos (noncoloring)	860	15
Tonics, dressings, and other hair-grooming aids	549	9
Other hair preparations	276	6
Blushers (all types)	238	2
Face powders	250	3
Foundations	287	1
Lipstick	790	3
Other makeup preparations	135	2
Bath soaps and detergents	385	9
Deodorants (underarm)	250	1
Other personal cleanliness products	291	2
Aftershave lotion	216	1
Shaving cream	139	1
Other shaving preparations	60	1
Cleansing preparations	653	14
Depilatories	28	1
Face and neck preparations (excluding shaving preparations)	263	6
Body and hand preparations (excluding shaving preparations)	796	11
Moisturizing preparations	769	12
Night preparations	188	7
Paste masks (mud packs)	255	7
Skin fresheners	184	6
Other skin care preparations	692	19
Suntan gels, creams, and liquids	136	2
1998 Total uses of Calendula Extracts		**178**

Calendula Officinalis Extract and Calendula Officinalis do not appear in Annex II (list of substances which must not form part of the composition of cosmetic products), III (list of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down), or IV (list of coloring agents allowed for use in cosmetic products) of the Cosmetics Directive of the European Union (1995).

Noncosmetic

C. officinalis L. is generally recognized as safe (GRAS) in spices and other natural seasonings and flavorings (FDA 1997).

C. officinalis has been used in traditional herbal medicine (Gracza 1987), often because of its (reported) anti-inflammatory activity (Boucaud-Maitre, Algernon, and Raynaud 1988; Della Loggia et al. 1994; Bezákova et al. 1996).

TABLE 2
Concentration of use data (FDA 1984)

Product category	5%–10%	1%–5%	0.1%–1%	Unknown	Total
Calendula Officinalis Extract					
Wave sets				1	1
Face powders	1				1
Foundations		1			1
Shaving cream (aerosol/brushless/lather)				1	1
Face/body/hand preparations (excluding shaving)		1	5	7	13
Night preparations			2		2
Paste masks (mud packs)		1			1
Other skin care preparations			1	2	3
Suntan gels/creams/liquids				1	1
1984 Totals	1	3	8	12	24
Calendula Officinalis					
Lipstick		1			1
Moisturizing products			1		1
Paste masks (mud packs)		1			1
1984 Totals	0	2	1	0	3

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, Excretion

Published data on the absorption, distribution, metabolism, and excretion of Calendula Officinalis Extract and Calendula Officinalis were not found.

Dermal Effects

Standard skin wounds were induced on a depilated area of the backs of groups of 24 male Wistar rats, and the wounds were covered with 5% unguentum (control group), allantoin alone (control group), or unguentum with C_1 and C_5 fractions isolated from *C. officinalis* flowers and allantoin (test group) to determine the effects on epithelialization (Klouček-Papova et al. 1982). The test and control materials were applied daily. Epithelialization was determined on days 0, 1, 3, 5, 14, and 21, wound exudate was examined microscopically 8, 24, and 48 hours after wound infliction, and tissue samples from the wound were examined microscopically on day 10. There was "significantly more intensive epithelialization of the wounds" for animals of the control group as compared to animals of the test groups, especially by day 14. Microscopic examination of the exudate from test animals detected a greater glycogen content in the "polynuclears," a "considerable number" of blast cells at 24 hours, the presence of "numerous differentiated macrophages having a cytoplasm rich in various inclusions" after 48 hours, and that "lymphoid elements produce a more intensively nuclear (green) fluorescence" as compared with controls. At microscopic examination of the wound at day 10, a thinner leucocytic-necrotic torus was observed on the surface of the wound of test animals as compared to controls, and that "definite zones" of the wounds of test animals were almost entirely filled with granulation tissue, as opposed to insular development of granulation tissue in the wounds of control animals. Also, the amount of "mature collagen" fibers compared to "young collagen" fibers was much greater in the test than in the control animals.

Immunologic Effects

Wagner et al. (1985) reported the isolation of polysaccharides with molecular weights of 25,000 to >500,000 Da from an aqueous. NaOH extract of *Calendula officinalis* L. that had significant immunostimulating activities according to the granulocytes and carbon clearance tests.

Cytotoxicity

The cytotoxicity of five extracts of *C. officinalis* that had different compositions was evaluated using MRC5, Hep2, and Ehrlich cell lines (Boucaud-Maitre, Algernon, and Raynaud 1988). All the extracts were cytotoxic, but the activity using 0.2 to 0.02 g/l of the extracts varied from 30% to 99% killed cells using the MRC5 cell line, from 2% to 99% killed cells using the Hep2 cell line, and from 10% to 100% cells killed using the Ehrlich cell line. Using saline solution as a control, the percentage of killed cells varied from 16% to 20%, 2% to 4%, and 0% to 2% for the MRC5, Hep2, and Ehrlich cell lines, respectively. Antitumoral activity was also studied using the mouse Ehrlich carcinoma. One of the extracts was inactive and three were "poorly active," whereas "an absence of development of the ascites was observed" with the most saponin-rich extract.

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

The LD_{50} of Calendula Officinalis Extract for rats was >4640 mg/kg (CTFA 1980).

The LD_{50}, for rats, of a mixture containing Calendula Officinalis Extract (1%–5%), soybean (Glycine Soja) oil (>50%), and tocopherol (<0.1%) was >20 ml/kg (Chemisches Laboratorium Dr. Kurt Richter GmbH 1996).

Parenteral

Using two to three albino mice per group, the intraperitoneal (IP) LD_{50} of Calendula Officinalis Extract was determined to be 300 mg/kg (Dhar et al. 1968).

Short-Term Toxicity

Groups of dd-mice were given 5, 10, or 20 ml/kg of a mixture of Calendula Officinalis Extract, butylene glycol, and water (percentages not specified) for 14 days (Ichimaru Pharcos Co., Ltd. 1994). The LD_{50} was >20 ml/kg.

Subchronic Toxicity

Published data on the subchronic toxicity of Calendula Officinalis Extract and Calendula Officinalis were not found.

Chronic Toxicity

Published data on the chronic toxicity of Calendula Officinalis Extract and Calendula Officinalis were not found.

Dermal Irritation

The dermal irritation potential of 10% aqueous Calendula Officinalis Extract was determined in a single-insult occlusive patch test (SIOPT) using nine rabbits (CTFA 1983). Calendula Officinalis Extract, 10%, had a primary irritation index (PII) of 0.0 and was not an irritant.

An SIOPT was performed to determine the dermal irritation potential of an eye cream containing 1% Calendula Officinalis Extract (CTFA 1986a). The eye cream produced minimal irritation.

A mixture of Calendula Officinalis Extract (1%–5%), soybean (Glycine Soja) oil (>50%), and tocopherol (<0.1%), tested at 10% in liquid paraffin, was nonirritating to rabbits in a Draize test (Chemisches Laboratorium Dr. Kurt Richter GmbH 1996).

The irritation potential of a mixture containing Calendula Officinalis Extract, butylene glycol, and water (percentages not specified) was determined in a Draize test in which 0.5 ml of the mixture was applied to intact and abraded skin of six albino rabbits (Ichimaru Pharcos Co., Ltd. 1994). The test sites were scored 4, 24, and 48 hours after application. Very slight erythema was observed after 4 hours. The mixture, 0.5 ml, was also applied 19 times to the skin of five guinea pigs over a 4-week period. Erythema and edema were not observed.

Sensitization

The sensitization potential of Calendula Officinalis Extract was determined in a modified Magnusson-Kligman maximization test using 10 female Dunkin Hartley guinea pigs (CTFA 1984). During induction, intradermal injections of 0.05 ml of 50% aqueous Freund's complete adjuvant (FCA), 5% Calendula Officinalis Extract in propylene glycol, and 5% Calendula Officinalis Extract in 50% aqueous FCA were made to sites on the upper back of each animal. A control group of 10 animals received the injections without the test material. During the booster phase 1 week after induction, 20% Calendula Officinalis Extract (a dose determined to be slightly irritating) was applied to the induction site for 48 hours under an occlusive patch. Two weeks after application of the booster, the animals were challenged with 5% and 10% Calendula Officinalis Extract that was applied for 24 hours under an occlusive patch. The challenge sites were graded 24 and 48 hours after patch removal. Calendula Officinalis Extract, 5% or 10%, did not produce a sensitization reaction.

A mixture of Calendula Officinalis Extract (1%–5%), soybean (Glycine Soja) oil (>50%), and tocopherol (<0.1%) was not sensitizing to guinea pigs (Chemisches Laboratorium Dr. Kurt Richter GmbH 1996).

The sensitization potential of a 50% aqueous solution of a mixture containing Calendula Officinalis Extract, butylene glycol, and water (percentages not specified) was determined in a maximization test using guinea pigs (Ichimaru Pharcos Co., Ltd. 1994). Erythema and edema were not observed.

Photosensitization

The phototoxicity potential of a 50% aqueous solution of a mixture containing Calendula Officinalis Extract, butylene glycol, and water (percentages not specified) was determined using six guinea pigs (Ichimaru Pharcos Co., Ltd. 1994). One-tenth milliliter of the test article was applied and exposed to a 15-minute minimal erythema dose. The mixture was not phototoxic.

Ocular Irritation

The ocular irritation potential of 10% aqueous Calendula Officinalis Extract was determined in a study using six rabbits (CTFA 1983). The test article was instilled into the conjunctival sac of the eye of each animal, and the eyes were not rinsed. Calendula Officinalis Extract, 10%, produced minimal irritation.

The ocular irritation potential of eye creams containing 1% Calendula Officinalis Extract was also determined (CTFA 1986a). The eye creams produced no to minimal irritation.

A mixture of Calendula Officinalis Extract (1%–5%), soybean (Glycine Soja) oil (>50%), and tocopherol (<0.1%), tested at 10% in liquid paraffin, was nonirritating to rabbit eyes in a Draize test (Chemisches Laboratorium Dr. Kurt Richter GmbH 1996).

The ocular irritation potential of a mixture containing Calendula Officinalis Extract, butylene glycol, and water (percentages not specified) was determined in a Draize test in which 0.1 ml of the mixture was applied to the conjunctival sacs of six albino rabbits (Ichimaru Pharcos Co., Ltd. 1994). A conjunctival reaction was observed in one rabbit.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Published data on the reproductive and developmental toxicity of Calendula Officinalis Extract and Calendula Officinalis were not found.

GENOTOXICITY

An Ames test using *Salmonella typhimurium* TA98 was performed without and with metabolic activation to determine the mutagenic potential of six saponins isolated from the dried flowers of *C. officinalis* L. (Elias et al. 1990). The saponins, 80 to 200 μg/tube, were not mutagenic. The saponins, $\leq$400 μg, also were not toxic to *S. typhimurium* TA97, TA98, TA100, or TA102, without or with metabolic activation in a preliminary spot test.

A somatic mutation and recombination test using *Drosophila melanogaster* was performed to determine the genotoxic potential of 20% and 40% *C. officinalis* herbal tea extract (Graf et al. 1994). The *C. officinalis* tea was not genotoxic. Two flavonols, quercetin and rutin, had weak genotoxic activity.

CARCINOGENICITY

Published data on the carcinogenic potential of Calendula Officinalis Extract and Calendula Officinalis were not found.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation

The irritation potential of a cosmetic formulation containing 1% Calendula Officinalis Extract was performed using 14 subjects (CTFA 1986a). The cosmetic formulation had an irritation index (PII) of 0.

The cumulative irritation potential of a cosmetic formulation containing 1% Calendula Officinalis Extract was determined in a study completed using 13 subjects, 3 males and 10 females (Hilltop Research 1986). The test material, 0.2 ml, was applied to a site on the back of each subject for 23 hours under an occlusive patch daily for 20 days. The test sites were scored 1 hour after patch removal. A cosmetic formulation containing 1% Calendula Officinalis Extract was considered a "mild material."

In a 4-day minicumulative irritation test, a cosmetic eye product containing 1% Calendula Officinalis Extract applied under an occlusive patch had a PII of 0.24 (CTFA 1990). (Additional details not given.)

Sensitization

The sensitization potential of an eye cream containing 1% Calendula Officinalis Extract was determined in a repeated-insult patch test (RIPT) completed using 109 subjects, 11 males and 98 females (CTFA 1986b). The eye cream, 0.1 ml, was applied under an occlusive patch for 24 hours to a test site on the back of each subject 3 days per week for 3 weeks. Following a 2-week nontreatment period, a challenge patch was applied to a previously unpatched site for 24 hours. The site was scored 24 and 48 hours after patch removal. Erythematous reactions were not observed during induction or at challenge, and an eye cream containing 1% Calendula Officinalis Extract was not a sensitizer.

An RIPT of a cosmetic formulation containing 1% Calendula Officinalis Extract, using the same procedures described above, was completed using 102 subjects (TKL Research 1987). One subject had reactions at challenge indicative of a possible sensitization response. Upon rechallenge using occlusive and semiocclusive patches, the reactions were considered indicative of irritation and not sensitization. A cosmetic formulation containing 1% Calendula Officinalis Extract was not a sensitizer.

Predictive Testing

A multicenter sensitization study using 119 subjects with contact allergic dermatitis was performed according to internationally accepted methods using the European standard series and a number of cosmetic ingredients, including 10% Calendula extract in alcohol (de Groot et al. 1988). The test materials were applied for 2 days using van der Bend patch test chambers; the test sites were scored 20 minutes and 1 and 2 days after removal. Calendula extract caused a positive reaction in one subject.

A series of ointments, one of which contained calendula tincture, 10%, the European standard series, and the components of the ointment bases, that is, petrolatum, liquid paraffin, wool fat, and chlorophyll, were evaluated for their sensitization potential using 1032 subjects from six patch test clinics (Bruynzeel et al. 1992). Two subjects had positive reactions to the calendula tincture; one of these subjects also had a positive reaction to wool fat. The researchers stated that "the relevance of the patch test reactions is difficult to evaluate" because the subjects often do not know whether they have previously used the ointments. Also, "the number of reactions may be underestimated" because the ointment base may not be a suitable vehicle for testing.

A patch test was performed using 15 subjects according to the methods of the International Contact Dermatitis Research Group (ICDRG) with the European standard series and some Compositae allergens, including 10% calendula in petrolatum (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. Calendula, as both the plant extract and with pollen "as is," produced a positive result in one of 15 subjects. The flower of Calendula was tested "as is," either fresh or deep frozen for 6 months, and it produced a positive reaction in the one patient tested.

Commercial-grade absolute of calendula, 1% in petrolatum, was applied to three subjects that were "contact-sensitive" to numerous Compositae species and sesquiterpene lactones and to six eczema patients (Rodríquez and Mitchell 1977). (An absolute is a highly concentrated refined perfume material, usually liquid, that has undergone at least two extractions; it is obtained by alcohol extraction from concretes. A concrete is a solid, waxy material extracted from non- or low-resinous material; natural raw materials for concretes are usually prepared from vegetative

materials extracted from previously live tissue.) Positive reactions were not observed.

A sesquiterpene lactone mix, 0.1% petrolatum, was included in a standard patch test series and 686 patients were patch-tested with the series (Paulsen, Andersen, and Hausen 1993). Seventy-nine patients who had positive reactions to the mix or who were suspected of having a Compositae dermatitis were tested with a Compositae mix, 6% petrolatum. The test materials were applied under occlusive patches to the backs of the patients, and the sites were scored on days 2, 3, or 4, and sometimes on days 5 to 7, according to the methods of the ICDRG. Thirty-one patients had positive reactions to one or both mixes. One patient with Compositae allergy was patch tested with 10.0% *C. officinalis* L. had no response.

SUMMARY

Calendula Officinalis Extract is an extract of the calendula, *C. officinalis*, and Calendula Officinalis is a plant material derived from the flowers of the calendula. In 1998, it was reported to the FDA that Calendula Officinalis Extract was used in 178 cosmetic formulations; in 1984, it was used at concentrations of $\leq$10% and at unknown concentrations. Data submitted by the cosmetics industry reported that one company uses Calendula Officinalis Extract at concentrations of <0.5% in a styling gel, a shampoo, and a cream rinse, another company uses it at a concentration of 0.2 weight %, and a supplier reported that a mixture of Calendula Officinalis Extract (10% to 25%) and propylene glycol (>75%) is used at 1% to 10% in cosmetic products. Calendula Officinalis was not reported to be used.

The oral and IP LD_{50} values for rats and mice of Calendula Officinalis Extract were >4640 and 300 mg/kg, respectively. The oral LD_{50}, for rats, of a mixture containing Calendula Officinalis Extract, soybean (Glycine Soja) oil, and tocopherol and for mice, of a mixture containing Calendula Officinalis Extract, butylene glycol, and water was >20 ml/kg. In SIOPTs, Calendula Officinalis Extract, 10%, was nonirritating and an eye cream containing 1% Calendula Officinalis Extract was minimally irritating; mixtures that contained Calendula Officinalis Extract were not irritants. Calendula Officinalis Extract and mixtures containing Calendula Officinalis Extract were not sensitizers in tests using guinea pigs. A mixture containing Calendula Officinalis Extract, butylene glycol, and water was not phototoxic. Calendula Officinalis Extract, 10%, caused minimal ocular irritation, eye creams containing 1% Calendula Officinalis Extract caused no to minimal irritation, and mixtures containing Calendula Officinalis Extract produced no or little irritation.

Six saponins isolated from the dried flowers of *C. officinalis* L. were not mutagenic in an Ames test, and *C. officinalis* tea was not genotoxic in a somatic mutation and recombination test using *D. melanogaster*.

Clinical testing of cosmetic formulations containing 1% Calendula Officinalis Extract determined that the formulations were not very irritating. In RIPTs, cosmetic formulations containing 1% Calendula Officinalis Extract were not sensitizing. In predictive human patch testing, positive reactions to Calendula were seen in a small number of patients.

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 Calendula Officinalis Extract and Calendula Officinalis were insufficient to determine whether Calendula Officinalis Extract and Calendula Officinalis were either safe or unsafe. The Expert Panel released a Notice of Insufficient Data Announcement on June 6, 1997, outlining the data needed to assess the safety of Calendula Officinalis Extract and Calendula Officinalis. The types of data still required for each ingredient include[2]

1. Current concentration of use data.
2. Function in cosmetics.
3. UV absorption data; if absorption occurs in the UVA or UVB range, photosensitization data are needed.
4. Gross pathology and histopathology in skin and other major organ systems associated with repeated dermal exposures.[3]
5. Dermal reproductive/developmental toxicity data.[3]
6. Inhalation toxicity data, especially addressing the concentration, amount delivered, and particle size.
7. Genotoxicity testing in a mammalian system; if positive, a 2-year dermal carcinogenicity assay performed using National Toxicology Program (NTP) methods in needed.

The Expert Panel originally also requested information on the presence of contaminants. Some data were received and summarized in the report. The Expert Panel expects that pesticide residues would be kept to a minimum.

No offer to supply the needed 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 Calendula Officinalis Extract and Calendula Officinalis 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."

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