Final Report on the Safety Assessment of Arnica Montana Extract and Arnica Montana[1]

Arnica Montana Extract is an extract of dried flowerheads of the plant, *Arnica montana*. Arnica Montana is a generic term used to describe a plant material derived from the dried flowers, roots, or rhizomes of *A. montana*. Common names for *A. montana* include leopard's bane, mountain tobacco, mountain snuff, and wolf's bane. Two techniques for preparing Arnica Montana Extract are hydroalcoholic maceration and gentle disintegration in soybean oil. Propylene glycol and butylene glycol extractions were also reported. The composition of these extracts can include fatty acids, especially palmitic, linoleic, myristic, and linolenic acids, essential oil, triterpenic alcohols, sesquiterpene lactones, sugars, phytosterols, phenol acids, tannins, choline, inulin, phulin, arnicin, flavonoids, carotenoids, coumarins, and heavy metals. The components present in these extracts are dependent on where the plant is grown. Arnica Montana Extract was reported to be used in almost 100 cosmetic formulations across a wide range of product types, whereas Arnica Montana was reported only once. Extractions of Arnica Montana were tested and found not toxic in acute toxicity tests in rabbits, mice, and rats; they were not irritating, sensitizing, or phototoxic to mouse or guinea pig skin; and they did not produce significant ocular irritation. In an Ames test, an extract of *A. montana* was mutagenic, possibly related to the flavenoid content of the extract. No carcinogenicity or reproductive/developmental toxicity data were available. Clinical tests of extractions failed to elicit irritation or sensitization, yet Arnica dermatitis, a delayed type IV allergy, is reported in individuals who handle arnica flowers and may be caused by sesquiterpene lactones found in the flowers. Ingestion of *A. montana*–containing products has induced severe gastroenteritis, nervousness, accelerated heart rate, muscular weakness, and death. Absent any basis for concluding that data on one member of a botanical ingredient group can be extrapolated to another in the 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.

INTRODUCTION

The safety of Arnica Montana Extract and Arnica Montana as used in cosmetic formulations is reviewed in this report. Both Arnica Montana Extract and Arnica Montana are obtained from the arnica, *Arnica montana*, and serve as biological additives (Wenninger and McEwen 1997).

CHEMISTRY

Definition

Arnica Montana Extract (CAS Nos. 8057-65-6, 68990-11-4) is an extract of the dried flowerheads of the arnica, *A. montana* (Wenninger and McEwen 1997). Arnica Montana is a plant material derived from the dried flowers, roots, or rhizomes of *A. montana*. For information on extraction techniques, see Manufacture and Production below.

Arnica Montana Extract is also known as Arnica Extract; Extract of Arnica; Extract of Arnica Montana (Wenninger and McEwen 1997); Oils, Arnica Montana; Arnica Flower Oil; Arnica Montana Oil (Chemline 1996; Registry of the Toxic Effects of Chemical Substances [RTECS] 1996); and Arnica Oil (Chemline 1996). Arnica Montana is also know as Arnica (Wenninger and McEwen 1997). Common names for the flower *A. montana* are leopard's bane, mountain tobacco, mountain snuff, and wolf's bane (MacKinnon 1992).

Physical and Chemical Properties

Arnica Montana Extract is a dark brown clear liquid that has a pungent characteristic odor (Nikitakis and McEwen 1990). It is soluble in water and insoluble in mineral oil. Arnica Montana Extract has a specific gravity of 0.917 to 0.927 (25°/25°C) and a refractive index of 1.3735 to 1.3835 (25°C).

A mixture of Arnica Montana Extract (1%–5%), soybean (Glycine Soja) oil (>50%), and tocopherol (<0.1%) is yellow with a characteristic, aromatic odor (Chemisches Laboratorium Dr. Kurt Richter GmbH 1996). It is soluble in oils, has a refractive

Received 7 January 2001; accepted 21 March 2001.

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International Journal of Toxicology, 20(Suppl. 2):1–11, 2001

1091-5818/01 $12.00 + .00

index (n_D20°C) of 1.473 to 1.476, density (20°C) of 0.918 to 0.922 g/ml, and acid value of <3. A mixture of Arnica Montana Extract (10%–25%) and propylene glycol (>75%) is a clear, brown liquid with a faint herbal odor (Grau Aromatics GmbH & Co. 1997). It is soluble in water, has a refractive index of 1.425 to 1.445 (at 20°C), density of 1.030 to 1.050 (at 20°C), and a pH value of 5.5 to 6.5. A mixture of Arnica Montana Extract, butylene glycol, and water (percentages not specified) is a reddish-brown, transparent liquid with a characteristic odor (Ichimaru Pharcos Co., Ltd. 1995). It has a specific gravity (d20/20) of 1.01 to 1.05 and a pH of 6.0 to 7.0.

Arnica oil is a yellow aromatic liquid that is soluble in alcohol (Grant 1972). It has a density of 0.906, an acid value of 75.1, and a saponification value of 29.9.

Manufacture and Production

Arnica Montana Extract is prepared by the hydroalcoholic maceration and percolation of the dried flower heads of *A. montana* L, *Compositae*, and other *Arnica* species (Nikitakis and McEwen 1990).

A mixture containing Arnica Montana Extract (1%–5%), soybean (Glycine Soja) oil (>50%), and tocopherol (<0.1%) is characterized as a fatty oil extract from arnica blossoms extracted with soybean oil (Chemisches Laboratorium Dr. Kurt Richter GmbH 1996). The arnica blossoms are "gently disintegrated using a special technique, extracted with stabilized soybean oil, and finally filtered."

A mixture of Arnica Montana Extract (10%–25%) and propylene glycol (>75%) is prepared by extracting arnica flowers with 1,2-propylene glycol; the ratio of extract to botanical is 5:1 (Grau Aromatics GmbH & Co. 1997). A preservative, 0.6% phenonip (phenoxyethanol, methylparaben, butylparaben, ethylparaben, and propylparaben), is used.

A mixture of Arnica Montana Extract, butylene glycol, and water (percentages not specified) is prepared by extracting arnica flowers with 1,3-butylene glycol (Ichimaru Pharcos Co., Ltd. 1995).

Analytical Methods

The overall chromatographic pattern of the roots and flowers of *A. montana* L. was determined using thin-layer chromatography (TLC) and high performance liquid chromatography (HPLC) (Rossetti et al. 1987). The "purity" of *A. montana* flowers has been determined using TLC, HPLC, thermospray mass spectrometry, and micellar electrokinetic chromatography (Pietta et al. 1994).

Composition

A. montana contains up to 1% (normally about 0.3%) of a viscous volatile oil that is partly composed (approximately 50%) of fatty acids, especially palmitic, linoleic, myristic, and linolenic acids (Leung 1980). The dried flowerheads and the rhizomes and roots of *A. montana* contain 0.5% to 1% and 1.8% to 6.3%, respectively, of "essential oil"; 4-hydroxythymoldimethyl ether, a phenolic compound, comprises 46% of the oil. Other phenolic compounds, including thymol and thymol ethers, have been found in the flowers and subterranean organs. The subterranean organs yield an oil that consists of 54.3% linoleic acid, 17.4% palmitic acid, and 8% linolenic acid. The flowers contain seven flavones and nine flavonols, including apigenin, kaempferol, quercetin, tricin, and other derivatives. The flowers also contain 13 helenanolides, which are sesquiterpene lactones; these have been identified as helenalin, 11,13-dihydrohelenalin, and 11 ester derivatives (MacKinnon 1992). Flavonoids comprise 0.4% to 0.6% and sesquiterpene lactones comprise 0.3% to 0.9% of the flower (Woerdenbag et al. 1994).

Extract of *A. montana* in propylene glycol contained sugars, carotenoids, flavonoids, and essential oil components (Góra et al. 1980). Extract of *A. montana* in isopropyl myristate contained carotenoids, phenolic acids, sterols, and essential oil components.

A supplier of a mixture containing Arnica Montana Extract and propylene glycol stated that the plant is composed of essential oil, hydrocarbons, esters, ethers, alcohols, triterpenic alcohols, sesquiterpene lactones, sugars, phytosterols, phenol acids, tannins, choline, inulin, flavonoids, carotenoids, coumarins, and fatty acids (Grau Aromatics GmbH & Co. 1997). A supplier of a mixture containing Arnica Montana Extract and butylene glycol and water stated that the main elements of the plant are flavin, arnicin, phulin, and inulin (Ichimaru Pharcos Co., Ltd. 1995).

The components of arnica and their concentrations are dependent on where the plant is grown (Willuhn, Leven, and Luley 1994).

Impurities

A mixture of Arnica Montana Extract, butylene glycol, and water contains ≤10 ppm heavy metals and ≤1 ppm arsenic, and assay as crude saponin yields 0.1 to 0.2 w/v% (Ichimaru Pharcos Co., Ltd. 1995).

Ultraviolet Absorption

Published data on the ultraviolet absorption of Arnica Montana Extract and Arnica Montana were not found.

USE

Cosmetic

Arnica Montana Extract and Arnica Montana 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 Arnica Montana Extract was used in 97 cosmetic formulations, 95 uses under the name Arnica Extract and 2 uses under the name Arnica Oil, and that Arnica Montana was used in one cosmetic formulation (FDA 1998) (Table 1).

TABLE 1
Product formulation data (FDA 1998)

Product category	Total no. of formulations in category	Total no. containing ingredient
Arnica Montana Extract		
Bubble baths	200	1
Other fragrance preparations	148	1
Hair conditioners	636	4
Hair sprays (aerosol fixatives)	261	2
Shampoos (noncoloring)	860	4
Tonics, dressings, and other hair-grooming aids	549	9
Hair dyes and colors	1572	1
Blushers (all types)	238	1
Foundations	287	3
Cuticle softeners	19	1
Deodorants (underarm)	250	1
Aftershave lotion	216	1
Shaving cream	139	2
Cleansing preparations	653	6
Depilatories	28	1
Face and neck preparations (excluding shaving preparations)	263	4
Body and hand preparations (excluding shaving preparations)	769	11
Foot powders and sprays	35	1
Moisturizing preparations	769	7
Night preparations	188	6
Paste masks (mud packs)	255	3
Skin fresheners	184	9
Other skin care preparations	692	18
1998 Total uses of Arnica Montana Extract		97
Arnica Montana		
Body and hand preparations (excluding shaving preparations)	796	1
1998 Total uses of Arnica Montana		**1**

Concentration of use values are no longer reported to the FDA by the cosmetics industry (FDA 1992). One supplier reported that a mixture of Arnica Montana Extract (10%–25%) and propylene glycol (>75%) is used at 1% to 10% in cosmetic products (Grau Aromatics GmbH & Co. 1997). Another company stated that it uses Arnica Montana Extract at a concentration of 0.2 weight % (CTFA 1998). The product formulation data submitted to the FDA in 1984 stated that Arnica Montana Extract was used in 41 cosmetic formulations, with 38 uses under the name Arnica Extract and 3 uses under the name Arnica Oil, at concentrations of ≤5%. Arnica Montana, under the name Arnica, was reported to be used in one formulation at a concentration of ≤0.1%(FDA 1984) (Table 2).

International

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

Arnica Montana Extract and Arnica Montana do 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 (1995).

Noncosmetic

Arnica flowers, including *A. montana* L., are cleared for use as natural flavoring substances and natural substances used in conjunction with flavors when used in the minimum quantity required to produce the intended effect and in accordance with good manufacturing practice (FDA 1997).

TABLE 2
Concentration of use data (FDA 1984)

Product category	1%–5%	0.1%–1%	0%–0.1%	Unknown	Total
Arnica Montana Extract					
Bubble baths		1		1	2
Hair conditioners			1	1	2
Shampoos (noncoloring)			1	5	6
Tonics/dressings/other hair-grooming aids		1			1
Wave sets				1	1
Skin cleansing products (cold creams/lotions/liquids/pads)		2		1	3
Face/body/hand preparations (excluding shaving preparations)	1	2		6	9
Moisturizing products	1	1			2
Night preparations		2			2
Skin fresheners		2		2	4
Other skin care preparations	1	3		5	9
1984 Totals	3	14	2	22	41
Arnica Montana					
Skin fresheners			1		1
1984 Total			1		1

The *German Pharmacopeia* has a monograph on arnica flowers (Willuhn 1991). *A. montana* L. is used in traditional and homeopathic medicine (Duke 1985; Puhlmann, Zenk, and Wagner 1991), and is considered to have antiseptic, antiphlogistic, analgesic, and anti-inflammatory properties (Willuhn 1986). Arnica Montana Extract (as arnica oil) is used in liniments (Grant 1972). Arnica Montana (as arnica) is used as a topical counterirritant (Budavari 1989). Arnica extract can be found in teas, liqueurs, wound dressings, and in dentistry (Hausen 1980).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, Excretion

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

Immunologic Effects

Two immunologically active polysaccharides were isolated from the nutrition medium of *A. montana* cell cultures (Puhlmann, Zenk, and Wagner 1991). One polysaccharide, an acidic arabino-3,6-galactan-protein with mean molecular weight of 100,000 Da, had a pronounced anticomplementary effect and stimulated macrophages to secrete tumor necrosis factor. The other polysaccharide, a neutral fucogalactoxyloglucan with mean molecular weight of 22,500 Da, caused a strong enhancement of the serum elimination rate of intravenously administered carbon particles in vivo. A low-molecular-weight oligosaccharide isolated from the herb *A. montana* did not have immunological activity. Wagner et al. (1985) also reported the isolation of polysaccharides with molecular weights of 25,000 to >500,000 Da from an aqueous extract of *A. montana* L. that had significant immunostimulating activities according to the granulocytes and carbon clearance tests; polysaccharide from Arnica montana flowers increased phagocytosis 44% compared to control values.

A component of arnica flowers, helanin, "intervenes in various metabolic processes that play a role in inflammatory processes" (Willuhn 1991).

Hematologic Effects

Using human blood samples, two sesquiterpene lactones isolated from *A. montana* L., helenalin and 11α,13-dihydrohelenalin, inhibited collagen-induced platelet aggregation in a dose-dependent manner at 3 to 300 μM and helenalin inhibited arachidonic acid–induced platelet aggregation in a dose-dependent manner at 60 to 300 μM (Schröder et al. 1990). Inhibition of platelet activation was due to interaction with cellular sulfhydryl groups. Both sesquiterpene lactones inhibited thromboxane formation in platelets stimulated with collagen, but not in those stimulated with arachidonic acid.

Cytotoxicity

The cytotoxicity of the flavonoids and sesquiterpene lactones present in *Arnica* was evaluated using GLC_4, a human small cell lung carcinoma cell line, and COLO 320, a human colorectal cancer cell line, in the microculture tetrazolium assay (Woerdenbag et al. 1994). After continuous incubation, most of the flavonoids had low to moderate toxicity, with the concentrations that allowed a 50% survival in the range of 17 to >200 μM. Continuous incubation with the sesquiterpene lactones caused a

3- to 10-fold increase in cytotoxicity. The concentrations of the most cytotoxic sesquiterpene lactone, helenalin, that allowed 50% survival were 0.44 μM against GLC_4 and 1.0 μM against COLO 320.

ANIMAL TOXICOLOGY

Acute Toxicity

Dermal

Five grams per kilogram arnica resinoid, which is found in *A. montana*, was applied to the skin of five rabbits (Research Institute for Fragrance Materials, Inc. [RIFM] 1996a). Resinoids are extracts of gums, balsams, resins, or roots that consist in whole or in part of resinous materials. Slight irritant effects were observed and the dermal LD_{50} of arnica resinoid was >5 g/kg for rabbits.

Oral

The oral LD_{50} of Arnica Montana Extract in rats was >5 g/kg (Cosmetic, Toiletry, and Fragrance Association [CTFA] 1981).

The oral LD_{50} of Arnica Montana Extract was 123 mg/kg for mice (RTECS 1996).

The oral toxicity of a mixture consisting of Arnica Montana Extract (1%–5%), soybean (Glycine Soja) oil (>50%), and tocopherol (<0.1%) (Henkel Corporation 1997) was determined using groups of five male and five female SPF-Wistar rats (International Bio-Research, Inc. [IBR] 1972a). The animals were given one oral dose of 10, 15, or 20 ml/kg of the test mixture, and were observed for 14 days. None of the animals died during the study, and signs of toxicity were not observed. The acute oral LD_{50} of the mixture was >20 ml/kg for SPF-Wistar rats.

Ten rats were given 5 g/kg arnica resinoid orally (RIFM 1996a). No effects were observed and the oral LD_{50} of arnica resinoid was >5 g/kg for rats.

Parenteral

The intraperitoneal (IP) LD_{50} of Arnica Montana Extract was 31 mg/kg for mice (RTECS 1996).

Short-Term Toxicity

The oral toxicity of a mixture containing Arnica Montana Extract, butylene glycol, and water (percentages not specified) was determined by giving groups of dd-mice 10, 20, or 30 ml/kg of the mixture for 14 days (Ichimaru Pharcos Co., Ltd. 1995). One mouse of the 30-ml/kg group died. The oral LD_{50} was >20 ml/kg.

Subchronic Toxicity

Published data on the subchronic toxicity of Arnica Montana Extract and Arnica Montana were not found.

Chronic Toxicity

Published data on the chronic toxicity of Arnica Montana Extract and Arnica Montana were not found.

Dermal Irritation

The irritation potential of 50% Arnica Montana Extract, 5% in corn oil and undiluted, was determined in single insult occlusive patch tests using nine rabbits (CTFA 1981). Arnica Montana Extract, 50%, was practically nonirritating when applied at concentrations of 5% and 100%.

The irritation potential of a mixture consisting of Arnica Montana Extract (1%–5%), soybean (Glycine Soja) oil (>50%), and tocopherol (<0.1%) (Henkel Corporation 1997), applied as a 10% paraffin oil solution, was determined using six New Zealand white rabbits (IBR 1976). The hair was clipped from the back of each animal, and one test site was abraded and one was left intact. A dose of 0.5 ml was applied to each site for 24 hours under an occlusive patch. The test sites were scored for irritation according to the Draize scale 24 and 72 hours after dosing. Irritation was not observed at the intact or abraded sites, and the total primary irritation index (PII) was 0.

Groups of six rabbits were used in single occlusive patch tests to determine the irritation potential of two face creams containing 1% of a mixture of Arnica Montana Extract and sunflower (Helianthus Annuus) seed oil (CTFA 1986). The face creams had PIIs of 1.17 and 1.5 and were mildly and minimally irritating, respectively.

The irritation potential of a mixture containing Arnica Montana 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. 1995). The test sites were scored 4, 24, and 48 hours after application of the test article. Irritation was not observed. 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.

The irritation potential of 5% to 50% arnica absolute in 80% ethanol/20% distilled water was determined using four guinea pigs, two per sex (RIFM 1996b). (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.) The test materials were applied to the flank of each animal for 6 hours under an occlusive patch. The sites were scored for irritation 24 and 48 hours after patch removal. “Slight patchy to moderate erythema” was observed with 5%, 10%, and 25% arnica absolute and “slight patchy erythema” was observed with 50% arnica absolute.

The dermal irritation potential of 0.5% to 100% arnica absolute in diethyl phthalate (DEP) was determined in a similar study using four guinea pigs per dose; four patches were placed

on each animal (RIFM 1996b). The following were observed: 0.5% and 1.0%—no effects; 2.5%—slight patchy erythema in one animal; 5% and 10%—slight patchy erythema after 24 hours in two animals; 25%—slight to moderate patchy erythema; 50%—slight patchy erythema; 100%—slight patchy erythema.

Six male Skh:HR mice were used to determine the irritation potential of arnica absolute (RIFM 1996b). Twenty microliters were placed on a 5-cm^2 area of dorsal skin, and the test site was examined immediately after dosing and after 4, 24, and 48 hours. Irritation was not induced by 75% arnica absolute.

Six male Skh:HR mice were used to determine the irritation potential of 20% arnica resinoid in triethyl citrate in a similar study (RIFM 1996a). No effects were observed with 20% arnica resinoid.

Dermal Sensitization

The sensitization potential of Arnica Montana Extract was determined in a modified Magnusson-Kligman maximization test using a group of 10 female Hartley guinea pigs (CTFA 1981). The concentration used during induction was 5%. One week after induction, a "topical booster" of 10% sodium lauryl sulfate (SLS) was applied, and 24 hours later undiluted Arnica Montana Extract was applied to the same site for 48 hours under an occlusive patch. The animals were challenged 2 weeks after the booster with 5% and 10% Arnica Montana Extract in petrolatum. A negative-control group consisted of 10 female animals. Arnica Montana Extract was not a sensitizer.

The sensitization potential of a mixture consisting of Arnica Montana Extract (1%–5%), soybean (Glycine Soja) oil (>50%), and tocopherol (<0.1%) (Henkel Corporation 1997) was determined in an open epicutaneous test using 10 Pirbright white guinea pigs; a group of five guinea pigs was used as a control (IBR 1977). The hair on the left side of the back was clipped, and 0.5 ml of the mixture was applied to the test site daily for 10 days. Following a 14-day nontreatment period, the test material was applied to a previously untreated site on both test and control animals. The test sites were scored according to the methods of Draize 24 and 48 hours after application of the challenge dose. Signs of irritation were not observed following challenge, and the mixture of Arnica Montana Extract, Soybean (Glycine Soja) Oil, and Tocopherol was not a sensitizer.

The sensitization potential of a mixture containing Arnica Montana Extract, butylene glycol, and water (percentages not specified) was determined in a maximization test using guinea pigs (Ichimaru Pharcos Co., Ltd. 1995). Erythema and edema were not observed.

The sensitization potential of arnica absolute was determined in a Buehler sensitization test using 20 Hartley albino guinea pigs (RIFM 1996b). The induction dose was 25% arnica absolute in DEP. A vehicle-control group of 10 guinea pigs was used. The test animals were challenged with 1%, 3%, and 10% arnica absolute and the control animals were challenged with 3% and 10% arnica absolute and DEP. No effects were observed after challenge.

The sensitization potential of the raw extract and the tincture of *A. montana* L. was evaluated using 25 Pirbright white guinea pigs (Hausen 1978). Because 1% of the raw extract produced a primary toxic reaction, 0.5% was used. The researcher stated that "all animals could be sensitized" and that "*Arnica montana* is a very strong sensitizer."

An ether extract of *A. montana* L. was applied as a 10% solution daily to the shaved flanks of 10 female Pirbright guinea pigs for 10 days (Herrmann, Willuhn, and Hausen 1978). After a 2-week nontreatment period, challenge applications of 0.1%, 0.3%, and 1.0% of the raw extract was applied to the opposite flank of the animals. The researchers stated "a red spot with 0.1% dilution still demonstrated the attained sensitization." Two components of *A. montana*, helenalin and helenalinacetate, were then used as a challenge using five of the animals. After 24 hours, three, five, and five of the animals challenged with 0.1%, 0.3%, and 1% helenalin and two, one, and four of the animals challenged with 0.1%, 0.3%, and 1% helenalinacetate responded. The majority of the responses were slight spotted erythema; one animal challenged with 0.3% and one challenged with 1% helenalin had distinct erythema and two challenged with 1% helenalin had distinct confluent erythema and infiltration.

Drug material containing 0.1% to 0.5% arnica produced average reaction scores of 0.30 to 0.80, respectively (Hausen 1980).

Phototoxicity

The phototoxicity potential of a mixture containing Arnica Montana Extract, butylene glycol, and water (percentages not specified) was determined using six guinea pigs (Ichimaru Pharcos Co., Ltd. 1995). One-tenth milliliter of the test article was applied and exposed to a 15-minute minimal erythema dose. The mixture was not phototoxic.

Groups of six male Skh:HR hairless mice were used to determine the phototoxicity potential of arnica absolute in methanol (RIFM 1996b). Twenty microliters were applied to a 5-cm^2 area of dorsal skin. The test site was irradiated with a Xenon arc lamp 30 minutes after application and examined for irritation at 4, 24, 48, 72, and 96 hours. (Whether the output of the lamp was monitored was not stated.) A second group was irradiated with a black light lamp. Methanol and 8-methoxypsoralen (8-MOP) were used as the negative and positive controls, respectively. (Results for the controls were not given.) No phototoxic effects were observed with 75% arnica absolute.

A similar study was conducted to determine the phototoxicity of 20% arnica resinoid in triethyl citrate (RIFM 1996a). One of six male Skh:HR mice died on day 2 of the study, but the death was not treatment-related. No effects were observed.

Undiluted arnica resinoid was applied to six hairless mice, and the test sites were irradiated for 60 minutes with a Xenon lamp (RIFM 1996a). Another group of six mice was irradiated with a black light lamp. The animals were examined at 4, 24, 48, 72, and 96 hours. Methanol and 8-MOP were used as the negative and positive controls, respectively. No effects were observed in the test animals.

Ocular Irritation

The ocular irritation potential of 50% Arnica Montana Extract was tested undiluted and at 5% concentration in corn oil (CTFA 1981). The test article was instilled into the conjunctival sac of the eye of six rabbits per study, and the eyes were not rinsed. Arnica Montana Extract, 50%, was nonirritating when tested at 5% and minimally irritating when instilled undiluted.

The ocular irritation potential of a mixture consisting of Arnica Montana Extract (1%–5%), soybean (Glycine Soja) oil (>50%), and tocopherol (<0.1%) (Henkel Corporation 1997) was determined using three New Zealand white rabbits (IBR 1972b). The undiluted mixture, 0.5 ml, was placed in the conjunctival sac of the left eye of each rabbit. (It was not stated whether the eye was rinsed.) The right eye was untreated and used as a control. The eyes were scored for irritation after 1, 2, 8, 24, 48, and 72 hours and 4, 5, 6, and 7 days. Reddening of the conjunctiva was observed for 24 hours and slight chemosis was observed after 2 hours for all animals; other changes were not observed. The researchers concluded that the mixture "caused no concern in regard to application in the vicinity of the eyes."

The ocular irritation potential of a mixture consisting of Arnica Montana Extract (1%–5%), soybean (Glycine Soja) oil (>50%), and tocopherol (<0.1%) (Henkel Corporation 1997) was also determined using six New Zealand white rabbits (Consumer Product Testing 1977). The mixture, 0.1 ml, was instilled into the conjunctival sac of the eye of each rabbit, and the eyes were not rinsed. The mixture containing Arnica Montana Extract was not an ocular irritant, with Draize scores of 1, 0, and 0/110 on days 1, 2, and 3, respectively.

Groups of three rabbits were used to determine the ocular irritation potential of two face creams containing 1% of a mixture of Arnica Montana Extract and sunflower (Helianthus Annuus) seed oil (CTFA 1986). The cream was instilled into the conjunctival sac of the eyes of the rabbits, and the eyes were not rinsed. In both studies, a face cream containing 1% of a mixture of Arnica Montana Extract and sunflower (Helianthus Annuus) seed oil was minimally irritating.

The ocular irritation potential of a mixture containing Arnica Montana Extract, butylene glycol, and water (percentages not specified) was determined in a Draize test in which 0.1 ml of the mixture was placed in the conjunctival sacs of three albino rabbits (Ichimaru Pharcos Co., Ltd. 1995). Conjunctival reactions were observed in two rabbits.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Published data on the reproductive and developmental toxicity of Arnica Montana Extract and Arnica Montana were not found.

GENOTOXICITY

The mutagenic potential of an extract of arnica (100 μl of extract contains 100 mg dried arnica) was determined in an Ames test using *Salmonella typhimurium* strains TA98 and TA100 (Göggelmann and Schimmer 1986). Ethanolic solutions of 10 to 400 μl were evaluated with and without metabolic activation. The arnica extract produced a two- to fourfold increase in the number of revertants, as compared to controls with *S. typhimurium* TA98 with and without metabolic activation and with *S. typhimurium* TA100 with metabolic activation; an increase was not seen with TA100 without metabolic activation. The researchers ascertained that the mutagenic effects could be ascribed to the flavonols that are present in arnica. (The researchers stated that "the origin of the plant is important for the presence of essential components" and results can differ based on the district of growth and the preparation of the extract.) Göggelmann (1986) stated that "it is not possible to extrapolate from the mutagenicity of a preparation of a single plant to that of a medicine consisting of several plants." This is because "although the same amount of mutagenic activity is present in some of the drugs, different mutagenic effects have been observed. Consequently, the mode of preparation and the presence of additional plants influence the mutagenic activities."

CARCINOGENICITY

Published data on the carcinogenic potential of Arnica Montana Extract and Arnica Montana were not found.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation

The irritation potential of a face cream containing 1% of a mixture of Arnica Montana Extract and sunflower (Helianthus Annuus) seed oil was determined in a single-insult occlusive patch test using 15 subjects (CTFA 1986). The face cream had a PII of 0.13.

The irritation potential of a mixture containing Arnica Montana Extract, butylene glycol, and water (percentages not specified) was determined in a Draize test in which the mixture was applied to 30 subjects and the test sites were scored 48 and 72 hours after application (Ichimaru Pharcos Co., Ltd. 1995). (Details not provided.) There was a "+" reaction for one subject at 48 hour, but there were no positive reactions at 72 hours.

A 4-day minicumulative irritancy assay was performed to determine the irritation potential of a body cream containing 1% of a mixture of Arnica Montana Extract and sunflower (Helianthus Annuus) seed oil (CTFA 1988). The face cream was applied under an occlusive patch. (Additional details were not given.) The body cream containing 1% of a mixture of Arnica Montana Extract and sunflower (Helianthus Annuus) seed oil had "acceptable irritancy results," with a PII of 0.43.

The irritation potential of 4% arnica resinoid was determined by applying the substance to the backs of 26 subjects in a 48-hour closed patch test (RIFM 1996a). No effects were observed.

Dermal Irritation/Sensitization

The irritation and sensitization potential of 4% arnica absolute was determined in a maximization study using 22 subjects (RIFM 1996b). No effects were observed.

Application of arnica flowers, especially in the tincture form (70% from 1 part flower and 10 parts ethanol), can result in edematous eczema with vesiculation (Willuhn 1991). Arnica dermatitis is an allergic contact dermatitis, i.e., a delayed-reaction type IV allergy (Willuhn 1986). Helenanolides, sesquiterpene lactones found in the flowers of *A. montana*, are considered the cause of contact dermatitis that often results after handling of the flowers (MacKinnon 1992).

Dermal Sensitization

The sensitization potential of a face cream containing 1% of a mixture of Arnica Montana Extract and sunflower (Helianthus Annuus) seed oil was determined in a maximization test completed by 25 subjects, 11 males and 14 females (Ivy Laboratories—KGL 1988). A pretest indicated that the test material was not irritating to any of the subjects; therefore, SLS was used during induction. During induction, approximately 0.1 ml of 1% SLS was applied to the arm of each subject under an occlusive patch for 24 hour. Upon removal of the SLS patch, an occlusive patch containing 0.1 ml of the face cream was applied to the site for 48 to 72 hours. The site was observed for irritation upon removal of the test patch; if irritation was not observed, an occlusive patch containing 1% SLS was applied to the site for 24 hours, followed by application of an occlusive patch containing the test material. This procedure was performed for a total of five induction applications. After a 10-day nontreatment period, an occlusive patch containing 0.1 ml of 10% SLS was applied for 1 hour to a previously untreated site on the opposite arm. An occlusive patch containing the test material was then applied to that site for 48 hours. The test site was scored 1 and 24 hours after patch removal. A face cream containing 1% of a mixture of Arnica Montana Extract and sunflower (Helianthus Annuus) seed oil did not induce a sensitization reaction in any of the subjects.

A repeated-insult patch test was completed using 93 subjects, 7 males and 86 females, to determine the sensitization potential of a skin cream containing 1% of a mixture of Arnica Montana Extract and sunflower (Helianthus Annuus) seed oil (CTFA No date). The face cream, 0.1 ml, was applied to an area on the back of each subject under an occlusive patch for 24 hours, 3 days per week, for 3 weeks. Following a 2-week nontreatment period, challenge patches were applied to a previously unpatched site. The sites were scored 24 and 48 hours after patch removal. Erythematous responses were not observed during induction or challenge, and a skin cream containing 1% of a mixture of Arnica Montana Extract and sunflower (Helianthus Annuus) seed oil 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% arnica 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 of the chambers. Arnica extract caused a positive reaction in one subject.

A series of ointments, one of which contained 10% arnica tincture, 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). Three subjects had positive reactions to the arnica ointment; two of these subjects also had positive reactions 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 Compositae mix consisting of a short ether extract of 0.5% *A. montana* L. and other species was included in a standard series and patch tested using 3851 subjects 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 International Contact Dermatitis Research Group (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, 44 (51.8%) reacted to *A. montana* L. Ten of the 85 subjects that were retested reacted to *A. montana* L. only.

A patch test was performed according to the methods of the ICDRG with the European standard series and some Compositae allergens, including 0.5% arnica in petrolatum, using 15 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. Arnica, as the plant extract, produced positive results in three subjects and with the pollen "as is" produced positive results in two subjects.

Commercial-grade resinoid of arnica, 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). Positive reactions were not observed. The researchers stated that the commercial extracts could have been free of significant amounts of the sesquiterpene lactones.

A sesquiterpene lactone mix, in 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, in 6% petrolatum that included a 0.5% ether extract of *A. montana* L. 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. Twenty-three of 32 patients with Compositae allergy were patch-tested with 0.5% arnica, but no positive reactions were observed. One patient was photopatch-tested with arnica; a positive reaction was not seen.

Case Reports

Numerous case reports have described sensitization reactions to *A. montana* L. (Rudzki and Grzywa 1977; Hausen, Hermann, and Willuhn 1978; Hausen 1979; Hausen 1980; Fernández de Corres 1984; Pirker et al. 1992; Machet et al. 1993; RIFM 1996b).

Toxicity

Arnica Montana–containing products taken internally have caused accelerated pulse, heart palpitations, shortness of breath, and death (MacKinnon 1992). The FDA has classified arnica as an unsafe herb because it contains two unidentified compounds responsible for inducing severe gastroenteritis, nervous disturbance, changes in pulse rate, intense muscular weakness, collapse, and death.

SUMMARY

Arnica Montana Extract is an extract of the dried flowerheads of the arnica, *A. montana,* and Arnica Montana is a plant material derived from the dried flowers, roots, and rhizomes of the arnica. In 1998, it was reported to the FDA that Arnica Montana Extract was used in 97 cosmetic formulations and Arnica Montana was used in 1 cosmetic formulation. One supplier reported that a mixture of Arnica Montana Extract (10%–25%) and propylene glycol (>75%) is used at 1% to 10% in cosmetic products and another company stated that it uses Arnica Montana Extract at a concentration of 0.2 weight %. In 1984, Arnica Montana Extract was reported to be used at concentrations of ≤5% and Arnica Montana was reported to be used at ≤0.1%.

The oral and IP LD_{50} values of Arnica Montana Extract were 123 and 31 mg/kg for mice, respectively. The oral LD_{50} values of a mixture consisting of Arnica Montana Extract, soybean (Glycine Soja) oil, and tocopherol and a mixture of Arnica Montana Extract, butylene glycol, and water were both >20 ml/kg. The dermal and oral LD_{50} values of arnica resinoid were >5 g/kg for rabbits and rats, respectively. In an irritation study using New Zealand albino rabbits, the PII of a 10% paraffin oil solution of a mixture consisting of Arnica Montana Extract, soybean (Glycine Soja) oil, and tocopherol was 0. A mixture of Arnica Montana Extract, butylene glycol, and water was not irritating to rabbits. Erythema was observed upon application to guinea pigs of arnica absolute under an occlusive patch. Open application of arnica absolute and arnica resinoid was not irritating to mouse skin. A mixture consisting of Arnica Montana Extract, soybean (Glycine Soja) oil, and tocopherol was not sensitizing to guinea pigs in an open epicutaneous sensitization test. A raw extract, an ether extract, and a tincture of *A. montana* L. produced sensitization reactions in Pirbright white guinea pigs. Arnica absolute was not sensitizing to Hartley albino guinea pigs in a Buehler sensitization test. A mixture containing Arnica Montana Extract, butylene glycol, and water was not phototoxic to guinea pigs, and arnica absolute and arnica resinoid were not phototoxic to hairless mice. A mixture consisting of Arnica Montana Extract, soybean (Glycine Soja) oil, and tocopherol caused some conjunctival redness for 24 hours and very light chemosis at 2 hours in one study and was nonirritating in another study using rabbits when applied to the conjunctival sacs; a mixture containing Arnica Montana Extract, butylene glycol, and water produced conjunctival reactions when placed in the conjunctival sacs of rabbits.

In an Ames test, an extract of arnica produced a mutagenic response; the researchers attributed the response to the flavonols that are present in arnica. However, the origin of the plant and the mode of preparation of the extract were considered to play a role in the mutagenic potential.

A face cream containing 1% of a mixture of Arnica Montana Extract and sunflower (Helianthus Annuus) seed oil had a PII of 0.13. No reactions to a mixture containing Arnica Montana Extract, butylene glycol, and water were seen 72 hours after application. Application of arnica resinoid to the back of 26 subjects in a closed patch test did not result in dermal irritation. Arnica absolute was not irritating or sensitizing in a maximization study. In predictive patch tests, arnica produced positive responses in some subjects. Numerous case reports describing sensitization reactions to *A. montana* L. exist in the published literature. Some toxic effects of Arnica Montana–containing products have been reported.

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 Arnica Montana Extract and Arnica Montana were insufficient to determine whether Arnica Montana Extract and Arnica Montana 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 Arnica Montana Extract and Arnica Montana. 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.

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

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 is 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 remaining 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 Arnica Montana Extract and Arnica Montana for use in cosmetic products.

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