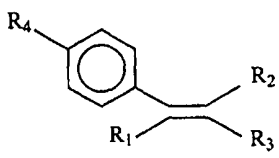




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 7/42	A1	(11) International Publication Number: WO 00/23044 (43) International Publication Date: 27 April 2000 (27.04.00)
(21) International Application Number: PCT/US99/23810 (22) International Filing Date: 13 October 1999 (13.10.99) (30) Priority Data: 09/174,177 16 October 1998 (16.10.98) US 09/263,013 5 March 1999 (05.03.99) US (71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventor: ROBINSON, Larry, Richard; 1114 Tumbleweed Drive, Loveland, OH 45140 (US). (74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217-1087 (US).		(81) Designated States: CN, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: UV PROTECTION COMPOSITIONS  (I) (57) Abstract The present invention relates to compositions suitable for providing protection against the harmful effects of ultraviolet radiation. The compositions provide excellent efficiency, broad spectrum UV efficacy and photostability. Methods of use for these compositions are also disclosed. The present compositions comprise: a) an effective amount of a UVA-absorbing dibenzoylmethane sunscreen active; b) an effective amount of a styrene derivative, having formula (I), wherein at least one of R₁, R₂ and R₃ is an electron-withdrawing substituent provided that R₁ is other than an aryl and that R₂ and R₃ together do not form a camphor group; and R₄ is selected from the group consisting of H, electron-donating substituents, and electron-withdrawing substituents other than an ether group or a cyano group; and c) a suitable carrier.		

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UV PROTECTION COMPOSITIONS

CROSS REFERENCE TO RELATED APPLICATION

5 This application is a Continuation-In-Part of Application Serial No. 09/174,177, filed October 16, 1998.

TECHNICAL FIELD

The present invention relates to compositions suitable for providing protection against the harmful effects of ultraviolet radiation having excellent efficiency, broad spectrum UV efficacy, and photostability. 10 The compositions comprise a UVA-absorbing dibenzoylmethane sunscreen active, a styrene derivative and a suitable carrier.

BACKGROUND OF THE INVENTION

It is well known that exposure to sunlight can pose a number of hazards to the skin. These damaging effects may result not only from sunbathing but also from the sunlight exposure associated with daily outdoor activities. The major short term hazard of prolonged exposure to sunlight is erythema, i.e., 15 sunburn, which primarily results from UVB radiation having a wavelength of from about 290 nm to about 320 nm. Over the long term, however, malignant changes in the skin surface often occur. Numerous epidemiologic studies demonstrate a strong relationship between sunlight exposure and human skin cancer. Another long term hazard of ultraviolet radiation is premature aging of the skin, which is primarily caused 20 by UVA radiation having a wavelength of from about 320 nm to about 400 nm. This condition is characterized by wrinkling and pigment changes of the skin, along with other physical changes such as cracking, telangiectasis, solar dermatoses, ecchymoses, and loss of elasticity. The adverse effects associated with exposure to UV radiation are more fully discussed in DeSimone, "Sunscreen and Suntan Products," *Handbook of Nonprescription Drugs*, 7th Ed., Chapter 26, pp. 499-511 (American Pharmaceutical 25 Association, Washington, D.C.; 1982); Grove and Forbes, "A Method for Evaluating the Photoprotection Action of Sunscreen Agents Against UV-A Radiation," *International Journal of Cosmetic Science*, 4, pp. 15-24 (1982); and U. S. Patent No. 4,387,089, DePolo, issued June 7, 1983.

As a result of the abovementioned hazards associated with sunlight exposure, the general public's interest in the sun protection product market has grown considerably. Today, there are not only sunscreen 30 products for sunbathing but there are also a variety of personal care products containing sunscreens, particularly cosmetic type products which are worn daily. "Personal care products" refer to health and cosmetic beauty aid products generally recognized as being formulated for beautifying and grooming the skin and hair. For example, personal care products include sunscreen products (e.g., lotions, skin creams, etc.), cosmetics, toiletries, and over-the-counter pharmaceutical products intended for topical usage.

Many conventional sunscreen products, in particular, are deficient, however, due to their inability to provide efficacious protection against broad spectrum UV radiation, i.e., protection against both UVB and UVA radiation. Today, most commercially available sunscreen products are efficient at absorbing UV radiation in the 290 nm to 320 nm UVB region such that sunburn of the skin is prevented. They are less efficient when it comes to absorbing light which falls in the 320 nm to 400 nm UVA region, which leaves the skin vulnerable to premature skin aging. This deficiency is due in part to the limited number of UVA absorbing sunscreen actives which are both commercially available and approved for global use. One class of these sunscreen actives includes dibenzoylmethane compounds which provide broad spectrum UV protection and 4-tert-butyl-4'-methoxydibenzoylmethane, in particular, is also approved for global use. Unfortunately, these sunscreens tend to photodegrade upon exposure to UV radiation thereby reducing their UVA efficacy. Consequently, sunscreen products which include these compounds are typically more difficult to formulate due to the inherent lack of photostability of dibenzoylmethane compounds. One approach to stabilize these types of sunscreens is described in U. S. Serial No. 07/929,612, Deckner, filed August 13, 1992, involving the use of benzylidene camphor sunscreens to stabilize the dibenzoylmethane compound. Such compositions, however, are not currently approved for global use on humans.

Thus, there is a need for photostabilized compositions suitable for providing protection against the harmful effects of UV radiation to human skin. In particular, in the personal care industry, a need remains for sunscreen products having excellent photostability, efficiency, and which provide broad spectrum UV protection (i.e., against both UVA and UVB radiation) in a safe and economical manner.

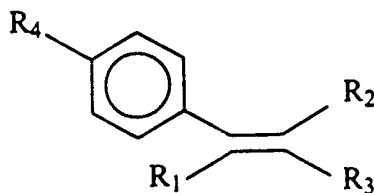
Likewise, in other industries such as the automotive care, marine vehicle care, household care, animal care, and coatings industries, UV radiation causes undesirable wear and damage. Therefore, a need exists for photostabilized compositions suitable for providing protection against the harmful effects of UV radiation to a variety of objects and/or materials prone to sun exposure.

It has surprisingly now been found that the compositions of the present invention, which comprise a UVA-absorbing dibenzoylmethane sunscreen active, a styrene derivative, and a suitable carrier, provide excellent photostability, efficiency, and UV protection efficacy (including both UVA and UVB protection), in a safe and economical manner.

SUMMARY OF THE INVENTION

The present invention relates to a composition suitable for providing protection against the harmful effects of ultraviolet radiation comprising:

- a) an effective amount of a UVA-absorbing dibenzoylmethane sunscreen active;
- b) an effective amount of a styrene derivative having the formula



wherein at least one of R_1, R_2 , and R_3 is an electron-withdrawing substituent provided that R_1 is other than an aryl and that R_2 and R_3 together do not form a camphor group; and R_4 is selected from the group consisting of H, electron-donating substituents, and electron-withdrawing substituents other than an ether group or a cyano group; and

5 c) a suitable carrier.

In preferred embodiments, the UVA-absorbing dibenzoylmethane sunscreen active and the styrene derivative are present in "safe and effective" amounts and the mole ratio of the UVA-absorbing dibenzoylmethane sunscreen active to the styrene derivative is from about 8:1 to about 1:1, more preferably from about 4:1 to about 1:1, and most preferably from about 2:1 to about 1:1. The present invention also relates to methods for providing protection to skin from the harmful effects of UV radiation by topical application of such compositions. Furthermore, the present invention relates to methods of stabilizing a UVA-absorbing dibenzoylmethane sunscreen active.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the present invention are useful for providing protection against the harmful effects of ultraviolet radiation, especially to human skin. The essential components of these compositions are described below. Also included is a nonexclusive description of various optional and preferred components useful in embodiments of the present invention.

The present invention can comprise, consist of, or consist essentially of any of the required or optional ingredients and/or limitations described herein.

20 All percentages and ratios are calculated on a weight basis unless otherwise indicated. All percentages are calculated based upon the total composition unless otherwise indicated.

All molar weights are weight average molecular weights and are given in units of grams per mole.

All ingredient levels are in reference to the active level of that ingredient, and are exclusive of solvents, by-products, or other impurities that may be present in commercially available sources, unless otherwise indicated.

25 All measurements made are at ambient room temperature, which is approximately 73°F, unless otherwise designated.

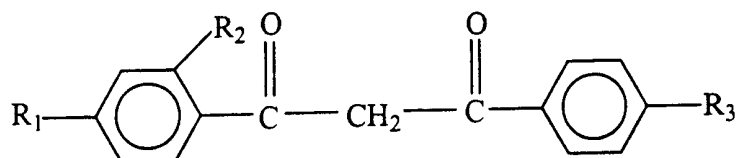
All documents referred to herein, including patents, patent applications, and printed publications, are hereby incorporated by reference in their entirety in this disclosure.

30 By "safe and effective amount" is meant an amount of a compound, component, or composition (as applicable) sufficient to significantly induce a positive effect (e.g., photoprotection or improvement in photostability), but low enough to avoid serious side effects, (e.g., undue toxicity or allergic reaction), i.e., to provide a reasonable benefit to risk ratio, within the scope of sound medical judgment.

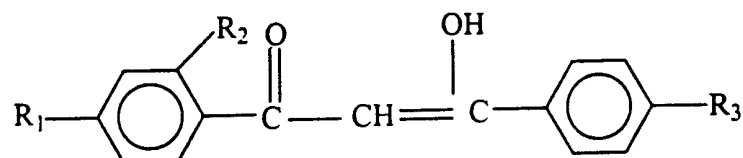
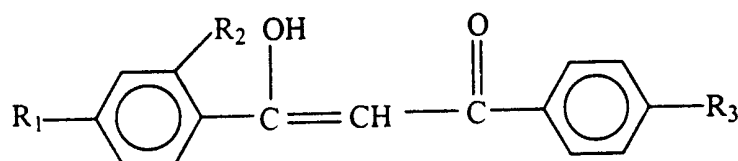
35 By "effective amount" is meant an amount of a compound, component, or composition (as applicable) sufficient to significantly induce a positive effect (e.g., photoprotection or improvement in photostability).

UVA-Absorbing Dibenzoylmethane Sunscreen Active

The compositions of the present invention comprise a UVA-absorbing dibenzoylmethane sunscreen active which absorbs UV radiation having a wavelength of from about 320 nm to about 400 nm. Preferred UVA-absorbing dibenzoylmethane sunscreen actives have the general structure



wherein R_1 is a substituent selected from the group consisting of H, OR, and NRR wherein each R is independently H, or $\text{C}_1 - \text{C}_{20}$ straight or branched alkyls, R_2 is selected from the group consisting of H or OH, and R_3 is selected from the group consisting of H, or $\text{C}_1 - \text{C}_{20}$ straight or branched alkyls. Even though the dibenzoylmethane chromophore is represented as a 1,3-diketone, it should be understood that this representation in no way excludes other tautomeric forms of the functional group such as the enol form. Thus, whenever the 1,3-diketone form is designated, it is understood that all appropriate enol tautomers are also contemplated and included herein. These tautomeric enol forms of the dibenzoylmethane chromophore can be represented by the following tautomeric structures.



wherein R_1 , R_2 , and R_3 are defined as above. Examples of such UVA-absorbing dibenzoylmethane sunscreen actives are described in U. S. Patent No. 4,489,057, issued to Welters et al. on December 18, 1984 and U. S. Patent No. 4,387,089, issued to Depolo on June 7, 1983; and in *Sunscreens: Development, Evaluation, and Regulatory Aspects*, edited by N. J. Lowe and N. A. Shaath, Marcel Dekker, Inc. (1990).

Suitable UVA-absorbing dibenzoylmethane sunscreen actives include, but are not limited to, those selected from the group consisting of 2-methyldibenzoylmethane, 4-methyldibenzoylmethane, 4-isopropyldibenzoylmethane, 4-tert-butyldibenzoylmethane, 2,4-dimethyldibenzoylmethane, 2,5-dimethyldibenzoylmethane, 4,4'-diisopropylbenzoylmethane, 4-tert-butyl-4'-methoxydibenzoylmethane, 2-methyl-5-isopropyl-4'-methoxydibenzoylmethane, 2-methyl-5-tert-butyl-4'-methoxydibenzoylmethane, 2,4-dimethyl-4'-methoxydibenzoylmethane, 2,6-dimethyl-4'-tert-butyl-4'-methoxydibenzoylmethane, and mixtures thereof. Preferred UVA-absorbing dibenzoylmethane sunscreen actives include those selected from the group consisting of 4-tert-butyl-4'-methoxydibenzoylmethane, isopropyldibenzoylmethane, and mixtures

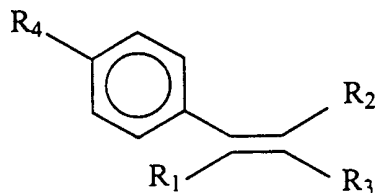
thereof. A more preferred UVA-absorbing dibenzoylmethane sunscreen active is 4-tert-butyl-4'-methoxydibenzoylmethane.

5 The sunscreen active, 4-tert-butyl-4'-methoxydibenzoylmethane, which is also known as butyl methoxydibenzoylmethane or Avobenzone, is commercially available under the names Parsol® 1789 from Givaudan-Roure (International) S.A. (Basel, Switzerland) and Eusolex® 9020 from Merck & Co., Inc. (Whitehouse Station, NJ). The sunscreen 4-isopropylidibenzoylmethane, which is also known as isopropyl dibenzoylmethane, is commercially available from Merck under the name Eusolex 8020.

10 The UVA-absorbing dibenzoylmethane sunscreen active of the instant invention is present in an effective amount, preferably in a safe and effective amount, to provide broad spectrum UV protection either independently or in combination with other UV protective actives which may be present in the composition. The composition preferably contains from about 0.01% to about 30%, more preferably from about 0.1% to about 6%, and most preferably from about 1% to about 3%, by weight of the composition, of the UVA-absorbing dibenzoylmethane sunscreen active. Exact amounts of the sunscreen active will vary depending upon the desired Sun Protection Factor, i.e., the "SPF" of the composition as well as the desired level of
15 UVA protection. (SPF is a commonly used measure of photoprotection of a sunscreen against erythema. The SPF is defined as the ratio of the ultraviolet energy required to produce minimal erythema on protected skin to that required to produce the same minimal erythema on unprotected skin in the same individual. See *Federal Register*, 43, No. 166, pp. 38206-38269, August 25, 1978).

Styrene Derivative

The compositions of the present invention also comprise a styrene derivative having the formula



wherein at least one of R_1 , R_2 , and R_3 is an electron-withdrawing substituent provided that R_1 is other than an aryl and that R_2 and R_3 together do not form a camphor group. In the above chemical formula, R_4 is selected from the group consisting of H, electron-donating substituents, and electron-withdrawing substituents other than an ether group or a cyano group. In any case, preferably, the electron-withdrawing substituent of R_1 , R_2 , and R_3 is selected from the group consisting of CN, COOH, COOR', CONH₂, CONHR', CONR'₂, CHO, COR', SO₂R', SO₂OR', NO, and an aryl wherein R' is a C₁ - C₃₀ straight chain or branched alkyl or an aryl. When R_4 is an electron-withdrawing substituent, it is selected from the group consisting of COOH, COOR', CONH₂, CONHR', CONR'₂, CHO, COR', SO₂R', SO₂OR', NO, and an aryl wherein R' is a C₁ - C₃₀ straight chain or branched alkyl or an aryl. On the other hand, the electron-donating substituent is preferably selected from the group consisting of R', NR'₂, NHR', NH₂, NHCOR', OH, OCOR', SR', SH, I, Cl, F, Br and an aryl wherein R' is a C₁ - C₃₀ straight chain or branched alkyl or an aryl.

As used herein, "alkyl" means carbon-containing chains which may be straight, branched or cyclic; substituted or unsubstituted; saturated, monounsaturated (i.e. one double or triple bond in the carbon chain), or polyunsaturated (i.e. two or more double bonds in the carbon chain, two or more triple bonds in the carbon chain, one or more double and one or more triple bonds in the carbon chain). Unless otherwise indicated, alkyl are preferably as follows. Preferred alkyl are straight or branched chain, more preferably straight chain. Preferred alkyl are mono-, di-, or tri- substituted, or unsubstituted, most preferably unsubstituted. Preferred alkyl are saturated or monounsaturated and, if so, preferably with a double bond; more preferably alkyl are saturated. Preferred alkyls are C₁-C₃₀, more preferably C₁-C₁₀, also more preferably C₁-C₄, even more preferably methyl, ethyl and t-butyl, even still more preferably methyl and ethyl, and most preferably methyl.

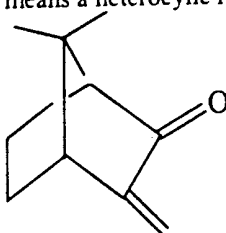
Thus the term "substituted alkyl" is included in the definition of alkyl. Preferred alkyl substituents (i.e. substitution on alkyls) include ester, ketone, aldehyde, carboxylic acid, halo, aryl, amino, hydroxy, alkoxy, cyano, nitro, amino (including mono- and disubstituted amino), thiol, and substituted thiol and trifluoromethyl. More preferred alkyl substituents are ester and aryl.

As used herein the term "alkoxy" includes the above described alkyl radicals attached to the molecule via oxygen. Thus, alkyl not only includes the C₁-C₁₀ alkoxy, but also includes species such as methylenedioxy, ethylenedioxy and other similarly bifunctional, or multifunctional alkoxy substituents. These multifunctional substituents can be attached to various places in the molecule and thus form bridged species. For example, species such as dioxolanes, dioxanes and the like are specifically contemplated.

As used herein "halo" means F, Cl, Br, and I. Preferred "halos" are F, Cl, and Br, more preferably F and Cl, most preferably F.

As used herein, "aryl" or "Ar" means aromatic rings which may be unsubstituted or substituted. Preferred aryl are phenyl or naphthyl, especially phenyl. Preferred aryl are mono-, di-, tri- substituted or unsubstituted; more preferred aryl are monosubstituted or unsubstituted, most preferred being unsubstituted. Preferred aryl substituents include ester, ketone, aldehyde, carboxylic acid, alkyl, halo, amino, hydroxy, alkoxy, cyano, nitro and trifluoromethyl. More preferred aryl substituents are alkyl and ester. The most preferred aryl is unsubstituted and thus is phenyl.

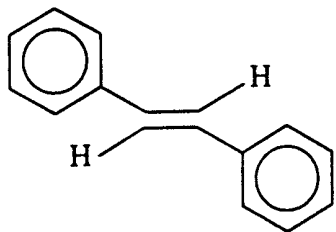
As used herein, "camphor group" means a heterocyclic ring having the formula



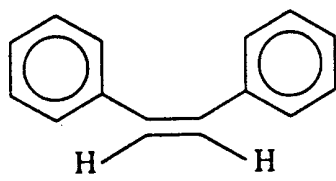
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Preferred styrene derivatives are selected from the group consisting of:

e-stilbene

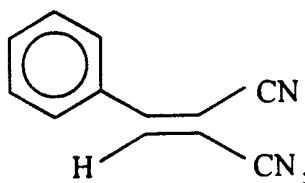


z-stilbene

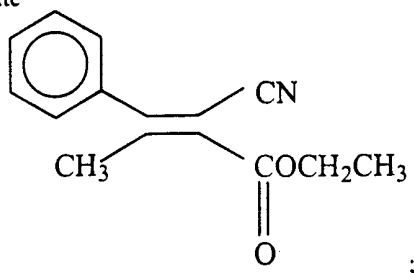


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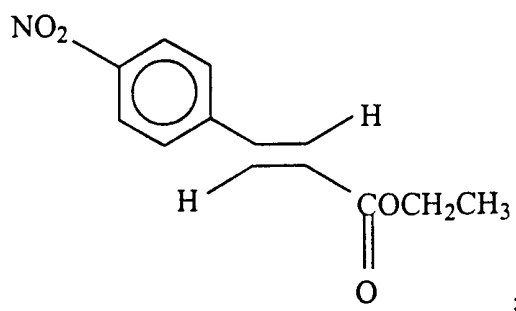
benzylidene malonitrile



ethyl-2-cyano-3-phenyl-2-butenate

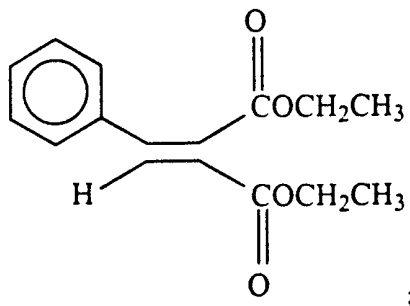


ethyl-4-nitrocinnamate

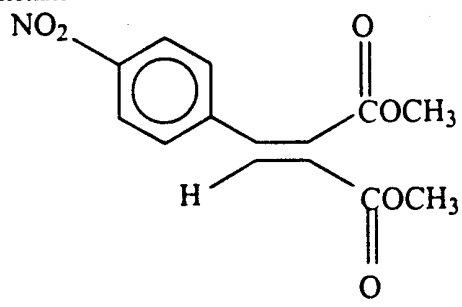


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diethyl benzalmonate



dimethyl-4-nitrobenzylidene malonate



10 and mixtures thereof. More preferably, the styrene derivative is selected from the group consisting of e-stilbene, z-stilbene, benzylidene malonitrile, ethyl-2-cyano-3-phenyl-2-butenate, diethyl benzalmonate, and mixtures thereof. Most preferably, the styrene derivative is diethyl benzalmonate. Suitable styrene derivatives are commercially available from Aldrich Chemical Co., Inc. (Milwaukee, WI).

15 The styrene derivative of the present invention is present in an effective amount, preferably in a safe and effective amount, to reduce the photodegradation of the UVA-absorbing dibenzoylmethane sunscreen

active. Photodegradation may be determined by a reduction of the UV absorption capability which in turn may be measured by using standard UV absorption methods. Preferred compositions retain at least about 75%, more preferably at least about 85%, and most preferably at least about 95%, of their initial UV absorption after irradiation with approximately 2 J/cm² per desired SPF unit of broad band UV radiation, e.g., 30 J/cm² for an SPF 15 composition. Preferably, the styrene derivative is present in an amount such that the mole ratio of the UVA-absorbing dibenzoylmethane sunscreen active to the styrene derivative is preferably from about 8:1 to about 1:1, more preferably from about 4:1 to about 1:1, and most preferably from about 2:1 to about 1:1.

Carrier

The compositions of the present invention comprise a suitable carrier or vehicle for the UVA-absorbing dibenzoylmethane sunscreen active, the styrene derivative, and any optional components. Suitable carriers are well known in the art and are selected based on the end use application. For example, carriers of the present invention include, but are not limited to, those suitable for application to skin, hair, nails, animal skin, fur, automobiles, fabrics, marine vehicles, as well as those suitable for incorporation into plastics, metals, etc.. Preferably, the carriers of the present invention are suitable for application to skin (e.g., sunscreens, creams, milks, lotions, masks, serums, etc.); hair and fur (e.g., shampoos, hair setting or treatment gels or lotions, shaping/curling/fixation lacquers or lotions, etc.); and nails (e.g., polishes, treatments, etc.). In preferred embodiments, the carrier is suitable for application to skin which means that the carrier and its components are suitable for use in contact with skin, hair, fur, and nails without undue toxicity, incompatibility, instability, allergic response, and the like within the scope of sound medical judgment. Such carriers are well-known to one of ordinary skill in the art, and can include one or more compatible liquid or solid filler diluents or vehicles which are suitable for application to skin, hair, fur, and nails. The exact amount of carrier will depend upon the level of the UVA-absorbing dibenzoylmethane sunscreen active, the styrene derivative and any other optional ingredients which one of ordinary skill in the art would classify as distinct from the carrier (e.g., other active components). The compositions of the present invention preferably comprise from about 20% to about 99.8%, more preferably from about 50% to about 99%, and most preferably from 75% to about 95%, by weight of the composition, of a carrier.

The carrier and compositions herein can be formulated in a number of ways, including but not limited to emulsions (in emulsion technology, a composition comprising a "dispersed phase" and a "continuous phase;" the dispersed phase existing as small particles or droplets that are suspended in and surrounded by a continuous phase). For example, suitable emulsions include oil-in-water, water-in-oil, water-in-oil-in-water, oil-in-water-in-oil, and oil-in-water-in-silicone emulsions. Preferred compositions comprise an oil-in-water emulsion.

The compositions of the present invention can be formulated into a wide variety of product types, including creams, waxes, pastes, lotions, milks, mousses, gels, oils, tonics, and sprays. Preferred compositions are formulated into lotions, creams, gels, and sprays. These product forms may be used for a

number of applications, including, but not limited to, hand and body lotions, cold creams, facial moisturizers, anti-acne preparations, topical analgesics, make-ups/cosmetics including foundations, eyeshadows, lipsticks, and the like as well as coatings (e.g., paints, varnishes, polishes, adhesives, etc.), household care items (e.g., detergents, cleansers, fabric conditioners, etc.), automotive and marine vehicle
5 care items (e.g., waxes, etc.), hair care and styling products (e.g., shampoos, conditioners, gels, mousses, sprays, etc.), topical animal care items (e.g., shampoos, conditioners, skin treatments, etc.). Any additional components required to formulate such products vary with product type and can be routinely chosen by one skilled in the art.

If compositions of the present invention are formulated as an aerosol and applied to the skin as a
10 spray-on product, a propellant is added to the composition. Examples of suitable propellants include chlorofluorinated lower molecular weight hydrocarbons. A more complete disclosure of propellants useful herein can be found in Sagarin, Cosmetics Science and Technology, 2nd Edition, Vol. 2, pp. 443-465 (1972).

Optional Components

15 The compositions of the present invention may contain a variety of other ingredients such as are conventionally used in a given product type provided that they do not unacceptably alter the benefits of the invention.

In a preferred embodiment, where the composition is to be in contact with human skin, the optional components should be suitable for application to skin, that is, when incorporated into the composition they
20 are suitable for use in contact with human skin without undue toxicity, incompatibility, instability, allergic response, and the like within the scope of sound medical judgment. The *CTFA Cosmetic Ingredient Handbook*, Second Edition (1992) describes a wide variety of nonlimiting cosmetic and pharmaceutical ingredients commonly used in the skin care industry, which are suitable for use in the compositions of the present invention. Examples of these ingredient classes include: abrasives, absorbents, aesthetic
25 components such as fragrances, pigments, colorings/colorants, essential oils, skin sensates, astringents, etc. (e.g., clove oil, menthol, camphor, eucalyptus oil, eugenol, menthyl lactate, witch hazel distillate), anti-acne agents, anti-caking agents, antifoaming agents, antimicrobial agents (e.g., iodopropyl butylcarbamate), antioxidants, binders, biological additives, buffering agents, bulking agents, chelating agents, chemical additives, colorants, cosmetic astringents, cosmetic biocides, denaturants, drug astringents, external
30 analgesics, film formers or materials, e.g., polymers, for aiding the film-forming properties and substantivity of the composition (e.g., copolymer of eicosene and vinyl pyrrolidone), opacifying agents, pH adjusters, propellants, reducing agents, sequestrants, skin bleaching and lightening agents (e.g., hydroquinone, kojic acid, ascorbic acid, magnesium ascorbyl phosphate, ascorbyl glucosamine), skin-conditioning agents (e.g., humectants, including miscellaneous and occlusive), skin soothing and/or healing agents (e.g., panthenol
35 and derivatives (e.g., ethyl panthenol), aloe vera, pantothenic acid and its derivatives, allantoin, bisabolol, and dipotassium glycyrrhizinate), skin treating agents, thickeners, and vitamins and derivatives thereof.

The compositions of the present invention may contain one or more of such optional components. Preferred compositions optionally contain one or more materials selected from UVB sunscreen actives, anti-acne actives, vitamin compounds, skin treating agents, humectants, moisturizers, skin conditioners, thickening agents, structuring agents, and emulsifiers.

5 In any embodiment of the present invention, however, the actives useful herein can be categorized by the benefit they provide or by their postulated mode of action. However, it is to be understood that the actives useful herein can in some instances provide more than one benefit or operate via more than one mode of action. Therefore, classifications herein are made for the sake of convenience and are not intended to limit the active to that particular application or applications listed.

10 a) **UVB Sunscreen Active**

The compositions of the present invention may comprise one or more UVB sunscreen actives which absorb UV radiation having a wavelength of from about 290 nm to about 320 nm. As used herein the UVB sunscreen active means an active other than the UVA-absorbing dibenzoylmethane sunscreen active which itself may possess UVB absorption properties. The compositions comprise an amount of the UVB
15 sunscreen active which is safe and effective to provide UVB protection either independently or in combination with other UV protective actives which may be present in the composition, preferably from about 0.1% to about 30%, more preferably from about 0.5% to about 25%, and most preferably from about 1% to about 20% by weight of the composition.

A wide variety of UVB sunscreen actives, including both organic sunscreen actives and inorganic
20 physical sunblocks, are suitable for use herein. Nonlimiting examples of such sunscreen actives are described in U. S. Patent No. 5,087,445 issued February 11, 1992 to Haffey et al; and U. S. Patent Nos. 5,073,371 and 5,073,372, both issued on December 17, 1991 to Turner et al. Nonlimiting examples of suitable physical sunblocks are described in *CTFA International Cosmetic Ingredient Dictionary*, Sixth Edition, 1995, pp. 1026-28 and 1103.

25 Preferred UVB sunscreen actives are selected from the group consisting of 2-phenyl-benzimidazole-5-sulfonic acid, octyl methoxycinnamate, TEA salicylate, octyl salicylate, octyl dimethyl PABA, zinc oxide, titanium dioxide, and mixtures thereof. A preferred water-soluble organic sunscreen active is 2-phenyl-benzimidazole-5-sulfonic acid while preferred inorganic physical sunblocks are zinc oxide, titanium dioxide, and mixtures thereof. Salt and acid-neutralized forms of the acidic sunscreens are also useful
30 herein.

b) **Anti-Acne Actives**

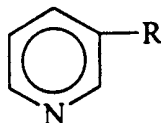
The compositions of the present invention may comprise one or more anti-acne actives. Examples of useful anti-acne actives include resorcinol, sulfur, salicylic acid, erythromycin, zinc, etc. Further examples of suitable anti-acne actives are described in further detail in U. S. Patent No. 5,607,980, issued to
35 McAtee et al, on March 4, 1997.

c) **Vitamin Compounds**

The compositions of the present invention may comprise vitamin compounds, precursors, and derivatives thereof. These vitamin compounds may be in either natural or synthetic form. Suitable vitamin compounds include, but are not limited to, Vitamin A (e.g., beta carotene, retinoic acid, retinol, retinoids, retinyl palmitate, retinyl propionate, etc.), Vitamin B (e.g., niacin, niacinamide, riboflavin, pantothenic acid, etc.), Vitamin C (e.g., ascorbic acid, etc.), Vitamin D (e.g., ergosterol, ergocalciferol, cholecalciferol, etc.), Vitamin E (e.g., tocopherol acetate, etc.), and Vitamin K (e.g., phytonadione, menadione, phthiocol, etc.) compounds.

In particular, the compositions of the present invention may comprise a safe and effective amount of a vitamin B₃ compound. Vitamin B₃ compounds are particularly useful for regulating skin condition as described in co-pending U. S. Application Serial No. 08/834,010, filed April 11, 1997 (corresponding to international publication WO 97/39733 A1, published October 30, 1997) which is incorporated by reference herein in its entirety. The compositions of the present invention preferably comprise from about 0.01% to about 50%, more preferably from about 0.1% to about 10%, even more preferably from about 0.5% to about 10%, and still more preferably from about 1% to about 5%, most preferably from about 2% to about 5%, of the vitamin B₃ compound.

As used herein, "vitamin B₃ compound" means a compound having the formula:



wherein R is - CONH₂ (i.e., niacinamide), - COOH (i.e., nicotinic acid) or - CH₂OH (i.e., nicotinyl alcohol); derivatives thereof; and salts of any of the foregoing.

Exemplary derivatives of the foregoing vitamin B₃ compounds include nicotinic acid esters, including non-vasodilating esters of nicotinic acid, nicotinyl amino acids, nicotinyl alcohol esters of carboxylic acids, nicotinic acid N-oxide and niacinamide N-oxide.

Examples of suitable vitamin B₃ compounds are well known in the art and are commercially available from a number of sources, e.g., the Sigma Chemical Company (St. Louis, MO); ICN Biomedicals, Inc. (Irvin, CA) and Aldrich Chemical Company (Milwaukee, WI).

The vitamin compounds may be included as the substantially pure material, or as an extract obtained by suitable physical and/or chemical isolation from natural (e.g., plant) sources.

d) **Skin Treating Agent**

The compositions of the present invention may contain one or more skin treating agents. Suitable skin treating agents include those effective for preventing, retarding, arresting, and/or reversing skin wrinkles. Examples of suitable skin treating agents include, but are not limited to, alpha-hydroxy acids such as lactic acid and glycolic acid and beta-hydroxy acids such as salicylic acid.

e) **Structuring Agent**

The compositions of the present invention may contain a structuring agent such as are known in the art. Structuring agents are particularly preferred in the oil-in-water emulsions of the present invention. Without being limited by theory, it is believed that the structuring agent assists in providing rheological characteristics to the composition which contribute to the stability of the composition. For example, the structuring agent tends to assist in the formation of the liquid crystalline gel network structures. The structuring agent may also function as an emulsifier or surfactant. Preferred compositions of this invention comprise from about 0.5% to about 20%, more preferably from about 1% to about 10%, most preferably from about 1% to about 5%, of one or more structuring agents.

The preferred structuring agents of the present invention are selected from the group consisting of stearic acid, palmitic acid, stearyl alcohol, cetyl alcohol, behenyl alcohol, stearic acid, palmitic acid, the polyethylene glycol ether of stearyl alcohol having an average of about 1 to about 21 ethylene oxide units, the polyethylene glycol ether of cetyl alcohol having an average of about 1 to about 5 ethylene oxide units, and mixtures thereof. More preferred structuring agents of the present invention are selected from the group consisting of stearyl alcohol, cetyl alcohol, behenyl alcohol, the polyethylene glycol ether of stearyl alcohol having an average of about 2 ethylene oxide units (steareth-2), the polyethylene glycol ether of stearyl alcohol having an average of about 21 ethylene oxide units (steareth-21), the polyethylene glycol ether of cetyl alcohol having an average of about 2 ethylene oxide units, and mixtures thereof. Even more preferred structuring agents are selected from the group consisting of stearic acid, palmitic acid, stearyl alcohol, cetyl alcohol, behenyl alcohol, steareth-2, steareth-21, and mixtures thereof.

f) **Thickening Agent (including thickeners and gelling agents)**

The compositions of the present invention can comprise one or more thickening agents, preferably from about 0.1% to about 5%, more preferably from about 0.1% to about 3%, and most preferably from about 0.25% to about 2%, by weight of the composition.

Nonlimiting classes of thickening agents include those selected from the group consisting of:

(i) **Carboxylic Acid Polymers**

These polymers are crosslinked compounds containing one or more monomers derived from acrylic acid, substituted acrylic acids, and salts and esters of these acrylic acids and the substituted acrylic acids, wherein the crosslinking agent contains two or more carbon-carbon double bonds and is derived from a polyhydric alcohol. Polymers useful in the present invention are more fully described in U. S. Patent No. 5,087,445, to Haffey et al, issued February 11, 1992; U. S. Patent No. 4,509,949, to Huang et al, issued April 5, 1985; U. S. Patent No. 2,798,053, to Brown, issued July 2, 1957; and in *CTFA International Cosmetic Ingredient Dictionary*, Fourth Edition, 1991, pp. 12 and 80.

Examples of commercially available carboxylic acid polymers useful herein include the carbomers, which are homopolymers of acrylic acid crosslinked with allyl ethers of sucrose or pentaerythritol. The carbomers are available as the Carbopol® 900 series from B.F. Goodrich (e.g., Carbopol® 954). In addition, other suitable carboxylic acid polymeric agents include copolymers of C₁₀₋₃₀ alkyl acrylates with

one or more monomers of acrylic acid, methacrylic acid, or one of their short chain (i.e., C₁₋₄ alcohol) esters, wherein the crosslinking agent is an allyl ether of sucrose or pentaerythritol. These copolymers are known as acrylates/C₁₀₋₃₀ alkyl acrylate crosspolymers and are commercially available as Carbopol® 1342, Carbopol® 1382, Pemulen TR-1, and Pemulen TR-2, from B.F. Goodrich. In other words, examples of
5 carboxylic acid polymer thickeners useful herein are those selected from the group consisting of carbomers, acrylates/C_{10-C₃₀} alkyl acrylate crosspolymers, and mixtures thereof.

(ii) Crosslinked Polyacrylate Polymers

The compositions of the present invention can optionally comprise crosslinked polyacrylate polymers useful as thickeners or gelling agents including both cationic and nonionic polymers, with the
10 cationics being generally preferred. Examples of useful crosslinked nonionic polyacrylate polymers and crosslinked cationic polyacrylate polymers are those described in U. S. Patent No. 5,100,660, to Hawe et al., issued March 31, 1992; U. S. Patent No. 4,849,484, to Heard, issued July 18, 1989; U. S. Patent No. 4,835,206, to Farrar et al, issued May 30, 1989; U.S. Patent No. 4,628,078 to Glover et al issued December 9, 1986; U.S. Patent No. 4,599,379 to Flesher et al issued July 8, 1986; and EP 228,868, to Farrar et al,
15 published July 15, 1987.

(iii) Polyacrylamide Polymers

The compositions of the present invention can optionally comprise polyacrylamide polymers, especially nonionic polyacrylamide polymers including substituted branched or unbranched polymers. Most preferred among these polyacrylamide polymers is the nonionic polymer given the CTFA designation
20 polyacrylamide and isoparaffin and laureth-7, available under the Tradename Sepigel 305 from Seppic Corporation (Fairfield, NJ).

Other polyacrylamide polymers useful herein include multi-block copolymers of acrylamides and substituted acrylamides with acrylic acids and substituted acrylic acids. Commercially available examples of these multi-block copolymers include Hypan SR150H, SS500V, SS500W, SSSA100H, from Lipo
25 Chemicals, Inc., (Patterson, NJ).

(iv) Polysaccharides

A wide variety of polysaccharides are useful herein. "Polysaccharides" refer to gelling agents which contain a backbone of repeating sugar (i.e., carbohydrate) units. Nonlimiting examples of polysaccharide gelling agents include those selected from the group consisting of cellulose, carboxymethyl
30 hydroxyethylcellulose, cellulose acetate propionate carboxylate, hydroxyethylcellulose, hydroxyethyl ethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, methyl hydroxyethylcellulose, microcrystalline cellulose, sodium cellulose sulfate, and mixtures thereof. Also useful herein are the alkyl substituted celluloses. In these polymers, the hydroxy groups of the cellulose polymer is hydroxyalkylated (preferably hydroxyethylated or hydroxypropylated) to form a hydroxyalkylated cellulose which is then
35 further modified with a C_{10-C₃₀} straight chain or branched chain alkyl group through an ether linkage. Typically these polymers are ethers of C_{10-C₃₀} straight or branched chain alcohols with

hydroxyalkylcelluloses. Examples of alkyl groups useful herein include those selected from the group consisting of stearyl, isostearyl, lauryl, myristyl, cetyl, isocetyl, cocoyl (i.e. alkyl groups derived from the alcohols of coconut oil), palmityl, oleyl, linoleyl, linolenyl, ricinoleyl, behenyl, and mixtures thereof. Preferred among the alkyl hydroxyalkyl cellulose ethers is the material given the CTFA designation cetyl
5 hydroxyethylcellulose, which is the ether of cetyl alcohol and hydroxyethylcellulose. This material is sold under the tradename Natrosol® CS Plus from Aqualon Corporation (Wilmington, DE).

Other useful polysaccharides include scleroglucans comprising a linear chain of (1-3) linked glucose units with a (1-6) linked glucose every three units, a commercially available example of which is Clearogel™ CS11 from Michel Mercier Products Inc. (Mountainside, NJ).

10 (v) Gums

Other thickening and gelling agents useful herein include materials which are primarily derived from natural sources. Nonlimiting examples of these gelling agent gums include materials selected from the group consisting of acacia, agar, algin, alginic acid, ammonium alginate, amylopectin, calcium alginate, calcium carrageenan, carnitine, carrageenan, dextrin, gelatin, gellan gum, guar gum, guar
15 hydroxypropyltrimonium chloride, hectorite, hyaluroinic acid, hydrated silica, hydroxypropyl chitosan, hydroxypropyl guar, karaya gum, kelp, locust bean gum, natto gum, potassium alginate, potassium carrageenan, propylene glycol alginate, sclerotium gum, sodium carboxymethyl dextran, sodium carrageenan, tragacanth gum, xanthan gum, and mixtures thereof.

Preferred compositions of the present invention include a thickening agent selected from the group
20 consisting of carboxylic acid polymers, crosslinked polyacrylate polymers, polyacrylamide polymers, and mixtures thereof, more preferably selected from the group consisting of carboxylic acid polymers, polyacrylamide polymers, and mixtures thereof.

g) Humectants, Moisturizers, and Skin Conditioners

Preferred compositions optionally comprise one or more humectants, moisturizers, or skin
25 conditioners. A variety of these materials can be employed and each can be present at a level of from about 0.01% to about 20%, more preferably from about 0.1% to about 10%, and most preferably from about 0.5% to about 7%. These materials include, but are not limited to, guanidine; glycolic acid and glycolate salts (e.g. ammonium and quaternary alkyl ammonium); salicylic acid; lactic acid and lactate salts (e.g., ammonium and quaternary alkyl ammonium); aloe vera in any of its variety of forms (e.g., aloe vera gel);
30 polyhydroxy alcohols such as sorbitol, glycerol, hexanetriol, propylene glycol, butylene glycol, hexylene glycol and the like; polyethylene glycols; sugars and starches; sugar and starch derivatives (e.g., alkoxylated glucose); hyaluronic acid; lactamide monoethanolamine; acetamide monoethanolamine; and mixtures thereof. Also useful herein are the propoxylated glycerols described in U. S. Patent No. 4,976,953, to Orr et al, issued December 11, 1990.

35 Also useful are various C₁-C₃₀ monoesters and polyesters of sugars and related materials. These esters are derived from a sugar or polyol moiety and one or more carboxylic acid moieties. Such ester

materials are further described in, U. S. Patent No. 2,831,854, U. S. Patent No. 4,005,196, to Jandacek, issued January 25, 1977; U. S. Patent No. 4,005,195, to Jandacek, issued January 25, 1977, U. S. Patent No. 5,306,516, to Letton et al, issued April 26, 1994; U. S. Patent No. 5,306,515, to Letton et al, issued April 26, 1994; U. S. Patent No. 5,305,514, to Letton et al, issued April 26, 1994; U. S. Patent No. 4,797,300, to Jandacek et al, issued January 10, 1989; U. S. Patent No. 3,963,699, to Rizzi et al, issued June 15, 1976; U. S. Patent No. 4,518,772, to Volpenhein, issued May 21, 1985; and U. S. Patent No. 4,517,360, to Volpenhein, issued May 21, 1985.

g) Emulsifiers

The compositions of the present invention can comprise one or more emulsifiers, e.g., to reduce the interfacial tension between phases and improve the formulation and stability of an emulsion. Suitable emulsifiers include a wide variety of nonionic, cationic, anionic, and zwitterionic emulsifiers. See McCutcheon's, *Detergents and Emulsifiers*, North American Edition (1986), published by Allured Publishing Corporation; U. S. Patent No. 5,011,681 issued to Ciotti et al on April 30, 1991; U. S. Patent No. 4,421,769 issued to Dixon et al on December 20, 1983; and U. S. Patent No. 3,755,560 issued to Dickert et al on August 28, 1973.

Suitable emulsifier types include esters of glycerin, esters of propylene glycol, fatty acid esters of polyethylene glycol, fatty acid esters of polypropylene glycol, esters of sorbitol, esters of sorbitan anhydrides, carboxylic acid copolymers, esters and ethers of glucose, ethoxylated ethers, ethoxylated alcohols, alkyl phosphates, polyoxyethylene fatty ether phosphates, fatty acid amides, acyl lactylates, soaps and mixtures thereof.

Suitable emulsifiers include, but are not limited to, TEA stearate, DEA oleth-3 phosphate, polyethylene glycol 20 sorbitan monolaurate (polysorbate 20), polyethylene glycol 5 soya sterol, steareth-2, steareth-20, steareth-21, cetareth-20, PPG-2 methyl glucose ether distearate, ceteth-10, polysorbate 80, cetyl phosphate, potassium cetyl phosphate, diethanolamine cetyl phosphate, polysorbate 60, glyceryl stearate, PEG-100 stearate, and mixtures thereof. Preferred emulsifiers are steareth-2, steareth-21, TEA stearate, diethanolamine cetyl phosphate, potassium cetyl phosphate, and mixtures thereof. The emulsifier can be used individually or as a mixture of two or more and comprises from about 0.1% to about 10%, more preferably from about 0.15% to about 7%, and most preferably from about 0.25% to about 5% of the compositions of the present invention.

While a variety of optional components may be included in the present compositions, the compositions are substantially free of benzylidene camphor derivatives. As used herein, "substantially free of benzylidene camphor" means the present compositions comprise less than about 0.1% of benzylidene camphor. Preferred compositions comprise less than about 0.05% of benzylidene camphor. Most preferably, the compositions are essentially free of benzylidene camphor, i.e., they contain no detectable benzylidene camphor.

Methods For Providing Protection From UV Radiation

The compositions of the present invention are suitable for providing protection against the harmful effects of ultraviolet radiation, preferably in personal care products. More preferably, the compositions of the present invention are suitable for use as sunscreens to provide protection to human skin from the harmful effects of UV radiation which include, but are not limited to, sunburn and premature aging of the skin. The present invention therefore also further relates to methods of protecting human skin from the harmful effects of UV radiation. Such methods generally involve attenuating or reducing the amount of UV radiation which reaches the skin's surface. To protect the skin from UV radiation, a safe and effective (photoprotective) amount of the composition is topically applied to the skin. "Topical application" refers to application of the present compositions by spreading, spraying, etc. onto the surface of the skin. The exact amount applied may vary depending on the level of UV protection desired. From about 0.5 mg of composition per cm² of skin to about 25 mg of composition per cm² of skin are typically applied.

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations on the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

The following sunscreen products are representative of the present invention.

Examples	I	II	III	IV
Component				
	WT%	WT%	WT%	WT%
Water	QS100	QS100	QS100	QS100
Carbomer 980	-----	-----	0.50	0.50
Carbomer 954	0.20	0.20	-----	-----
Acrylates/C ₁₀₋₃₀ Alkyl Acrylate ¹	0.10	0.10	0.10	0.10
Disodium EDTA	0.05	0.05	0.05	0.05
Methyl Paraben	0.25	0.25	0.25	0.25
Glycerin	4.00	4.00	7.00	7.00
Octyl methoxycinnamate	-----	3.00	-----	-----
Octyl Salicylate	-----	-----	2.00	-----
Isopropyl myristate	6.00	6.00	6.00	6.00
Propyl Paraben	0.15	0.15	0.15	0.15
Diethylbenzalmalonate	2.00	2.50	-----	-----
Ethyl 2-Cyano-3-phenyl-2-butenate	-----	-----	0.70	1.50
4-t-Butyl-4'-methoxydibenzoylmethane	2.00	3.00	1.00	2.00
DEA Oleth-3 Phosphate	0.75	0.75	0.75	0.75
Stearic Acid	1.00	1.00	1.00	1.00
Cetyl Alcohol	1.00	1.00	1.00	1.00
Cetyl Palmitate	0.50	0.50	0.50	0.50
Triethanolamine	0.70	0.70	1.5	1.5

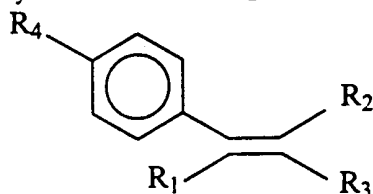
¹Available as Pemulen TR-1 from B.F. Goodrich

- 5 Prepare a water phase by combining the water, Carbomer 980 or Carbomer 954, acrylate copolymer, disodium EDTA, methyl paraben, and glycerin in an appropriate vessel with mixing and heating to 75°C. Prepare the oil phase by combining the octyl methoxycinnamate, octyl salicylate, isopropyl myristate, propyl paraben, diethylbenzalmalonate, ethyl 2-cyano-3-phenyl-2-butenate, 4-t-butyl-4'-methoxydibenzoylmethane, DEA oleth-3-phosphate, stearic acid, cetyl alcohol, and cetyl palmitate in a separate vessel with mixing and heating to 75°C. Next, mix the oil phase into the water phase with shearing to form an emulsion. Cool the emulsion with shearing to 60°C and add the triethanolamine. Slowly stir the emulsion and cool to 30 - 35°C and package as desired.
- 10

WHAT IS CLAIMED IS:

1. A composition suitable for providing protection against the harmful effects of ultraviolet radiation characterized in that said composition comprises:

- a) an effective amount of a UVA-absorbing dibenzoylmethane sunscreen active;
- b) an and effective amount of a styrene derivative having the formula

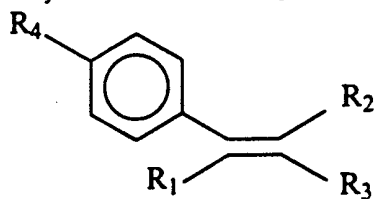


wherein at least one of R_1 , R_2 , and R_3 is an electron-withdrawing substituent provided that R_1 is other than an aryl and that R_2 and R_3 together do not form a camphor group, and R_4 is selected from the group consisting of H, electron-donating substituents, and electron-withdrawing substituents other than an ether group or a cyano group; and

- c) a suitable carrier.
2. The composition of Claim 1 wherein the UVA-absorbing dibenzoylmethane sunscreen active and the styrene derivative are present in a safe amount.
 3. The composition of any of the preceding claims wherein the electron-withdrawing substituent is independently selected from the group consisting of CN, COOH, COOR', CONH₂, CONHR', CONR'₂, CHO, COR', SO₂R', SO₂OR', NO, and an aryl wherein R' is a C₁ - C₃₀ straight chain or branched alkyl or an aryl.
 4. The composition of any of the preceding claims wherein the electron-donating substituent is independently selected from the group consisting of R', NR'₂, NHR', NH₂, NHCOR', OR', OH, OCOR', SR' SH, I, Cl, F, Br and an aryl wherein R' is a C₁ - C₃₀ straight chain or branched alkyl or an aryl.
 5. The composition of any of the preceding claims wherein the styrene derivative is selected from the group consisting of e-stilbene, z-stilbene, benzylidene malonitrile, ethyl-2-cyano-3-phenyl-2-butenate, ethyl-4-nitrocinnamate, diethyl benzalmalonate, dimethyl-4-nitrobenzylidene malonate, and mixtures thereof.
 6. The composition of any of the preceding claims wherein the UVA-absorbing dibenzoylmethane sunscreen active is selected from the group consisting of 2-methyldibenzoylmethane, 4-

methyldibenzoylmethane, 4-isopropyldibenzoylmethane, 4-tert-butyldibenzoylmethane, 2,4-dimethyldibenzoylmethane, 2,5-dimethyldibenzoylmethane, 4,4'-diisopropylbenzoylmethane, 4-tert-butyl-4'-methoxydibenzoylmethane, 2-methyl-5-isopropyl-4'-methoxydibenzoylmethane, 2-methyl-5-tert-butyl-4'-methoxydibenzoylmethane, 2,4-dimethyl-4'-methoxydibenzoylmethane, 2,6-dimethyl-4-tert-butyl-4'-methoxydibenzoylmethane, and mixtures thereof.

7. The composition of any of the preceding claims wherein the UVA-absorbing dibenzoylmethane sunscreen active is 4-tert-butyl-4'-methoxydibenzoylmethane.
8. The composition of any of the preceding claims wherein the composition comprises from about 0.01% to about 30%, by weight of the composition, of the UVA-absorbing dibenzoylmethane sunscreen active.
9. The composition of any of the preceding claims wherein the mole ratio of the UVA-absorbing dibenzoylmethane sunscreen active to the styrene derivative is from about 8:1 to about 1:1.
10. A method for providing protection against the harmful effects of ultraviolet radiation characterized in that said method comprises applying a safe and effective amount of the composition of any of the preceding claims to skin.
11. A method of stabilizing a UVA-absorbing dibenzoylmethane sunscreen active characterized in that said method comprises combining an effective amount of a UVA-absorbing dibenzoylmethane sunscreen active with an effective amount of a styrene derivative having the formula



wherein at least one of R_1 , R_2 , and R_3 is an electron-withdrawing substituent provided that R_1 is other than an aryl and that R_2 and R_3 together do not form a camphor group, and R_4 is selected from the group consisting of H, electron-donating substituents, and electron-withdrawing substituents other than an ether group or a cyano group.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/23810

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K7/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 195 39 189 A (BASF) 24 April 1997 (1997-04-24) example 2 ---	1-4,6-11
X	EP 0 848 947 A (L'OREAL) 24 June 1998 (1998-06-24) claim 1 ---	1-4,6-11
X,P	DE 197 55 650 A (BASF) 22 April 1999 (1999-04-22) the whole document ---	1-4,6-11
A	EP 0 658 341 A (3V SIGMA) 21 June 1995 (1995-06-21) the whole document ---	1-11
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

Special categories of cited documents:

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Date of the actual completion of the international search

13 January 2000

Date of mailing of the international search report

21/01/2000

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Fischer, J.P.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/23810

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	EP 0 590 998 A (SHISEIDO COMPANY LIMITED) 6 April 1994 (1994-04-06) the whole document ---	1-11
A	US 5 567 418 A (FORESTIER ET AL.) 22 October 1996 (1996-10-22) the whole document -----	1-11

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/23810

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99 /23810

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The group R4 is selected from the group consisting of H, electron-donating substituents, and electron-withdrawing substituents other than an ether group or a cyano group (see claim 1). Or in claim 4 the electron-donating substituent can be a group OR' wherein R' is C1-C30 straight chain or branched alkyl or an aryl. Even if R4 is an electron-withdrawing substituent, R4 can be a group CN (see claim 3).

The expressions electron-withdrawing substituent and electron-donating substituent are too broad and a complete search will not be possible.

Claims searched: 1-11 partially

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/23810

Patent document cited in search report	Publication date	Patent family members(s)	Publication date
DE 19539189 A	24-04-1997	AU 7290096 A CA 2231626 A CN 1200027 A WO 9715279 A EP 0857058 A US 5935563 A	15-05-1997 01-05-1997 25-11-1998 01-05-1997 12-08-1998 10-08-1999
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