

Photoprotection by Sunscreens with Topical Antioxidants and Systemic Antioxidants to Reduce Sun Exposure

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ABSTRACT: Skin cancer is the most common cancer diagnosed in the United States, and its incidence continues to rise. Epidemiological studies have documented that excessive sun exposure increases the risk of developing nonmelanoma skin cancer. Consequently, it is mandatory that the skin be protected from the damage that occurs from ultraviolet (UV) exposure. It is the purpose of this report to review the scientific basis for photoprotection by sunscreens, topical antioxidants, and systemic antioxidants to minimize the harmful effect of sun exposure. The US Food and Drug Administration regulates sunscreen products as over-the-counter drugs. Sunscreens are chemical or organic UV absorbers and nonchemical or inorganic UV absorbers. Other important sunscreen considerations include the sunscreen vehicle, sunscreen photostability, sunscreen preservatives, and sunscreen photoallergy and phototoxicity. Topical and systemic antioxidants have now been shown to supplement the photoprotective effects of sunscreen. The Skin Cancer Foundation, the only national and international nonprofit organization concerned exclusively with cancer of the skin, is playing a leadership role in eliminating skin cancer in our world.

KEY WORDS: Ultraviolet A I, Ultraviolet A II, Ultraviolet B, Ultraviolet C, ozone layer, sun protection factor, minimal erythema dose, ultraviolet index, sunscreen, vehicles, sunscreen photostability, sunscreen preservatives, sunscreen phototoxicity, The Skin Cancer Foundation, antioxidants, melanoma, squamous cell carcinoma, basal cell carcinoma, sunburn, photoaging, US Food and Drug Administration, photosensitivity

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I. INTRODUCTION

Skin cancer is the most common cancer diagnosed in the United States, and its incidence continues to rise. Epidemiological studies have documented that extensive sun exposure increases the risk of developing nonmelanoma skin cancer. Encouraging photoprotection is the leading preventative health strategy used in our country. There is an increased awareness of sun protection; however, occupation and lifestyle make total avoidance impossible. Because sunscreens are one of the most important photoprotective strategies, we are writing a collective review on the scientific basis for the use of sunscreen.

Because the electromagnetic radiation from the sun causes damage to the skin, the ultraviolet (UV) radiation that reaches the earth is reviewed. The earth is shielded by the ozone layer that filters and attenuates the sun's radiation. The adverse cutaneous and systemic reactions to sunlight in normal, healthy skin are classified into two types: the immediate type of sunburn and tanning, and the delayed type of long-term effects, including photoaging and photocarcinogenesis occur following exposure to the sun. To limit exposure to the sun's UV rays, The Skin Cancer Foundation, the American Academy of Dermatology, and the American Cancer Society have recommended that sun protection practices include the use of sunscreens with an SPF of 15 are the major focus of this review.

The US Food and Drug Administration (FDA) regulations of sunscreen products are discussed in detail as over-the-counter (OTC) drugs. Sunscreens have traditionally been divided into chemical or organic absorbers and nonchemical or inorganic absorbers on the basis of their mechanism of action. Other important considerations include the sunscreen vehicle, sunscreen photostability, sunscreen preservatives, and sunscreen photoallergy and phototoxicity. Topical and systemic antioxidants have now been shown to supplement the photoprotective effects of sunscreen. When considering any sun protection program, photosensitizing and photoallergic reactions and diseases must also be considered. The Skin Can-

cer Foundation, the only national and international foundation that is concerned exclusively with cancer of the skin, is playing a leadership role in developing a photopreventative strategy for eliminating skin cancer in our world. The mission of this nonprofit organization is reviewed in detail.

II. ELECTROMAGNETIC RADIATION FROM THE SUN

The sun's electromagnetic radiation (EMR), which emanates from its internal thermonuclear reactions, consists of both waves and particles. Waves are oscillations that travel through space and can be described in terms of frequency and wavelength. All EMR travels at the speed of light, and the frequency and wavelength are related by the equation:

$$C = \nu \times \lambda$$

where C = velocity of light (3×10^{10} cm/sec), ν = frequency (vibrations/sec), and λ = wavelength (cm).

The wavelengths emitted by the sun vary from an angstrom (Å) to hundreds of meters and are classified into the special regions shown in Table 1.

In addition to its transverse wave properties, EMR exhibits particle-like behavior in the form of tiny discrete packets of energy known as photons or quanta. The energy in a photon is directly proportional to the frequency of the radiation by the equation $E = h\nu$. Therefore, high-frequency radiation directly corresponds to high photon energy. UV is divided into the following regions: ultraviolet C (UVC 2000–2900 Å), ultraviolet B (UVB 2900–3200 Å), and ultraviolet A (UVA 3200–4000 Å). UVA is further divided into UVA II (UVA II 3200–3400 Å), or shortwave UVA, and UVA I (UVA I 3400–4000 Å), or long-wave UVA.

In 1998, the Centers for Disease Control and Prevention (CDC) indicated that overexposure to UV radiation is the most important behavioral risk factor for skin cancer.¹ This report listed measures to prevent skin cancer that included reducing direct exposure

TABLE 1. Classification of Solar Radiation

| Type of ray | Wavelength range |
|---------------------------|------------------|
| Cosmic rays | 0.005 Å |
| Gamma rays | 0.005–1.4 Å |
| X-rays | 0.1–100 Å |
| Vacuum ultraviolet | 10–2000 Å |
| Ultraviolet C (UVC) | 2000–2900 Å |
| Ultraviolet B (UVB) | 2900–3200 Å |
| Ultraviolet A (UVA) | 3200–4000 Å |
| Ultraviolet A II (UVA II) | 3200–3400 Å |
| Ultraviolet A I (UVA I) | 3400–4000 Å |
| Visible light | 4000–7400 Å |
| Near infrared | 7400 Å–1.5 nm |
| Middle infrared | 1.5–5.6 nm |
| Far infrared | 5.6–1000 nm |
| Microwaves and radiowaves | 1000 n–550 m |

to the sun, especially during midday hours (10 AM–4 PM). Wearing protective clothing (e.g., broad-brim hat, long-sleeve shirt, long pants, and sunglasses) and using sunscreens are recommended. They pointed out that people should also avoid artificial sources of UV radiation, such as tanning devices and sun lamps.² We are presently preparing separate collective reviews on new advances in photoprotection that include photoprotective clothing, photoprotective windows, and sunglasses that will be reported in separate reviews in this journal.

UVC has not been a factor to date in human cancers because it is sufficiently absorbed by the stratospheric ozone layer. However, both UVA and UVB reach the earth in abundant quantity in sunlight. In addition to causing cancer of the skin, UV radiation has been suggested to cause melanoma of the eye.³ Fortunately, the ozone layer still blocks most of the sun's harmful UVB rays from hitting the earth. Ozone depletion has been calculated to be 3–9% for temperate zones of both hemispheres.⁴ But with its rapid depletion by certain substances, such as synthetic industrial chemicals called *chlorofluorocarbons* (CFCs), the effects of

UVB are becoming an even greater concern.⁵ UVA, being a longer wavelength UV, penetrates deeper than UVB. Its output is relatively constant throughout the day. UVA is not filtered by window glass, is known to induce photoaging and photoimmunosuppression, and is within the action spectrum for the vast majority of drug-induced photosensitivity reactions. As such, it is recognized that protection from UVA exposure is equally important. If the ozone layer decreases by 5% over the next 20 years, there will be as much as a 10% increase in biologically effective radiation reaching the earth. It has been estimated that this heightened level of radiation could produce a 5–8% increase in melanomas, a 10% increase in basal cell carcinomas, and a 20% increase in squamous cell carcinomas over the next 20 years.

III. OZONE EFFECT

The earth is shielded by gases that filter and attenuate the sun's radiation. These gases are more commonly known as the *ozone layer*. About one-third of this energy is reflected, absorbed, or scattered by the atmosphere, allowing wavelengths between 2900 and 18,000 Å to reach the earth. Of the EMR waves that reach the earth, nearly half are in the visible light spectrum (4000–7400 Å). Although UV radiation constitutes only a percentage of the sun's total radiant energy, it is known to be responsible for skin cancers, photoaging, and cutaneous burns in humans.⁶

The overwhelming consensus in the scientific community is that environmental changes as a result of industrialization of the planet are responsible for decreasing the effectiveness of the ozone layer's ability to block UV radiation. Ozone acts as a selective filter that blocks UVC and part of UVB radiation. It has been calculated that ozone depletion is 3–9% for temperate zones for both hemispheres.^{7,8} A linear relationship between the decrease of the ozone layer and a concomitant increase in skin cancer has been shown, so that for every 1% decrease in the ozone layer, there is a corresponding increase of 1% in the incidence of skin-cancer-related mortality.⁹ Furthermore, it has

been suggested that for each 1% decrease in ozone, melanoma mortality enhances 1–2%.¹⁰ These findings are of particular concern in light of a New Zealand study that showed a 12% increase in UVB without a change in UVA levels over a 10-year period, apparently related to ozone depletion over that period.¹¹

Molina and Rowland⁵ found ozone depletion of the stratosphere in 1974 and suggested the role of CFCs as causal factors. In 1987, protocols were ratified in Montreal to reduce the production of ozone-depleting chemicals such as CFCs. Even though scientists agree on the severity of the problem of ozone depletion, the biological effects of CFCs are expected to continue into the future. CFCs are inert and will be present in the stratosphere for many years. Despite strong international agreements to reduce production of CFCs, these dangerous compounds continue to escape into the atmosphere from modern refrigeration and air-conditioning units.

IV. FACTORS EFFECTING RADIATION EXPOSURE

There are many factors that influence the magnitude of UV radiation. The altitude at which sun exposure occurs has considerable influence on the magnitude of UV radiation. When measured at sea level, UVR enhances 4% with each ascending 300-m interval of elevation.¹² Because higher altitudes have thinner atmospheres to absorb and reduce UVB radiation, skiers and mountain climbers are exposed to higher levels of UVB radiation than would be found at sea level.¹³ The composition of the earth's surface is another important consideration. For example, snow and ice reflect UVB radiation so that the amount of UVB radiation may be doubled. The reflection capability of light-colored sand of UVR is approximately $\frac{1}{3}$ as much as that reflected by snow and ice.¹⁴ In contrast, water does not effectively reflect UVR, allowing UVR to penetrate through water to a depth of 60 cm.

NOAA/National Weather Service, National Centers for Prediction (Camp Springs, Maryland) post a daily current UV Index forecast for the United

TABLE 2. UV Index

| Index scale | UV exposure level |
|-------------|-------------------|
| 0–2 | Very low |
| 3–4 | Low |
| 5–6 | Medium |
| 7–9 | High |
| 10+ | Very high |

The Skin Cancer Foundation recommends that all sun protection measures always be followed whenever outdoors.

States each day. The UV Index is a next-day forecast of the amount of skin-damaging UV radiation that is expected to reach the Earth's surface when the sun is highest in the sky (solar noon). It was created to advise people to make informed decisions about the amount of time they can spend in the sun. The UV Index uses a numerical scale to rate the strength of the sun's UV exposure level and recommend what sun protective measures to take. The height of the UV Index level can be correlated with the strength of the sun's UV radiation (Table 2). The Skin Cancer Foundation recommends that all sun protective measures be practiced whenever outdoors.

V. SKIN'S NATURAL DEFENSES

The human body has evolved several means to protect itself from UV radiation. The two most important are the thickening of the stratum corneum and the formation of melanin in melanocytes. Following exposure to UV radiation, the stratum corneum thickens by as much as three times in a biological process termed *epidermal hyperplasia*.¹⁵ This thickening occurs even in amelanotic skin and is associated with increased tolerance to subsequent exposure. These thick cell layers absorb, reflect, and scatter radiation. Consequently, the thick epidermal layers of the palms and soles display a greater tolerance to sun exposure than do the thinner epidermal layers that cover other anatomic regions.

While there are many substances in the skin capable of absorbing UV radiation, DNA and urocanic acid have been identified as being very important. DNA may absorb UVB (2900–3200 Å) directly causing changes between adjacent pyrimidine bases on one strand of DNA. These DNA changes are constantly being repaired by nucleotide excision repair. Whenever repair is incomplete, signature mutations may result that are characteristic of UV photodamage. These signature mutations have been detected in both squamous cell and basal cell carcinomas.

Urocanic acid has been considered to be another chromophore for UVA I absorption.¹⁶ Urocanic acid is a derivative of histidine produced by keratinocytes that is found in high concentrations superficially in the epidermis. Research indicates that isomerization of urocanic acid induced by UVB and UVA may contribute to photoaging of the skin.

Upon exposure to solar radiation, the melanocytic system undergoes two distinct changes. The first process, immediate pigment darkening (IPD) and persistent pigment darkening (PPD), results from photooxidation of existing melanin. This UV-induced pigment darkening fades within 20 minutes (for IPD) and 24 hours (for PPD); it contributes little to the development of a lasting tan, while it reduces the skin's tolerance for UV radiation energy. IPD and PPD do not offer any future photoprotection. The more important response of the pigmentary system is delayed tanning (DT), or true melanogenesis. DT is the skin's natural protection against UV-induced damage. However, it should be noted that UVB-induced tanning provides a protection factor of only 3, and UVA-induced tanning a protection factor of 1.3.¹⁷ In DT, the amount of melanin/melanocyte increases in a genetically determined capacity stimulated by UV radiation. This response is less well developed in children, explaining why they are more susceptible to sunburn.

An individual's skin color is determined genetically by a constitutive factor, the amount of melanin the skin contains, and a facultative factor, the ability of the skin to produce more melanin. The amount of melanin pigment in the skin determines the photosensitivity; consequently, dark-skinned individuals generally are

TABLE 3. Skin Types and Recommended Sunscreen Products

| Skin type | Response to Sun ^a | Sensitivity |
|-----------------|--|-------------|
| I ^b | Always burns easily; never tans | sensitive |
| II ^b | Always burns easily; tans minimally | sensitive |
| III | Burns moderately; tans gradually (light brown) | normal |
| IV | Burns minimally; tans well (moderate brown) | normal |
| V ^c | Rarely burns; tans profusely (dark brown) | insensitive |
| VI | Never burns (black) | insensitive |

^a After 35–40 minutes on previously unexposed skin.

^b Light-skinned, blue-eyed redheads, and some persons with dark brown hair and blue or green eyes.

^c Darker-skinned persons (e.g., those of Mediterranean or Asian-Indian descent).

more resistant to sunburn than are people with light complexions, though they are not entirely protected from the harmful effects of UV radiation. Approximately 15% of Caucasians do not produce sufficient melanin to protect them against sunburn. Upon exposure to the sun, distinct sites of hyperpigmentation (freckles) develop, leaving the remaining skin susceptible to burn. The Fitzpatrick skin phototype classification is a commonly used method to evaluate skin types and susceptibility to sunburn (Table 3).

VI. DISORDERS CAUSED BY SUNLIGHT IN HEALTHY PEOPLE

The adverse cutaneous and systemic reactions to sunlight in normal, healthy skin are classified into two types: the immediate type or acute sunburn, and the delayed type, long-term effects that occur following chronic exposure to light. Of solar UV radiation energy (measured in watts per square meter) that reaches the surface of the earth, 90–95% is UVA. Only 5–10% of the solar UV radiation energy is UVB. In addition to solar radiation, high-dose exposure can come from devices

such as sun beds/sunlamps, phototherapy, and PUVA therapy units.¹⁸ Because UVA has longer wavelengths than UVB, it penetrates more deeply into the skin. It has been estimated that about 19–50% of solar UVA can reach the depth of the melanocytes. In contrast, only 9–14% of solar UVB reaches the melanocytes. This long-wave-length property of UVA also allows it to pass through most automobile, office, and household windows, whereas UVB is blocked by window glass. The two UV spectra have markedly different biologic effects. For example, UVB is approximately 1000 times more effective than UVA in inducing erythema.¹⁹

VI.A. Acute Sunburn

After 48 hours of sun exposure, the UV energy absorbed at different levels of the skin results in cell damage in the dyskeratotic cells of the stratum malpighi and stratum corneum.²⁰ Erythema induced by vasodilation, increased blood flow, and edema ensues. An inflammatory infiltrate develops in the underlying papillary dermis, and is thought to be mediated by histamine, serotonin, and kinins. Prostaglandins (PG) and related derivatives have been implicated in the development of erythema, and increased levels of eicosanoids have been found in human tissue exposed to UV energy. These substances of low molecular weight are synthesized by microsomal enzymes in all mammalian cells, and the biosynthesis of PG can be inhibited by non-steroidal anti-inflammatory compounds, such as indomethacin or aspirin.

Depending on the skin type and duration of exposure, sunburn can range in severity from a mild asymptomatic erythema to a more intense skin reaction that includes exquisite tenderness, pain, swelling, and blistering. The most serious sunburn includes systemic signs such as fever, chills, nausea, and prostration.

VI.B. Treatment

Treatment of acute sunburn includes (1) restoring

any loss in intravascular volume, (2) suppressing UV radiation induced erythema, and (3) providing analgesics. When skin is burned by solar radiation, intravascular fluids extravasate into the burned tissue, thereby reducing intravascular volume. In extremely severe sunburn injuries, this reduction of vascular volume may be sufficient to produce hypotension. In such cases, the intravascular volume must be replaced with a crystalloid solution.

Most studies substantiate that synthesis and release of PG may be the primary mechanism in the production of erythema. PG synthetase inhibitors administered systemically or topically are highly efficient suppressors of UV erythema; they have to be administered within a few hours of sun exposure to be effective and have no apparent preventative effect on the ultimate damage to the skin. Aspirin and indomethacin have been used in the treatment of sunburn. In the laboratory, these drugs have been shown to reduce solar-simulated erythema.²¹ Because these experimental studies incorporated a topical application of indomethacin in a 2.5% solution, this observation suggests that oral aspirin and indomethacin may be valuable as well. These over-the-counter medications have been observed to suppress redness and relieve the burning sensation.

Topical steroids have also been used in the treatment of UV-induced erythema. Duteil et al.²² reported a randomized, double-blind study to evaluate topical corticosteroid treatments of sunburn. They evaluated the efficacy and safety of two topical glucocorticosteroids, 0.1% methylprednisolone (MPA) and 0.1% hydrocortisone 17-butyrate emulsion (HCB). The treatment sites were blinded and randomly assigned to both sides of the spine. The skin sites were then exposed to simulated sunlight radiation. The volunteers were subjected to the simulated sunlight twice daily for 7 days and evaluated daily with a 1-day follow-up. The treated areas had significantly lower sunburn reactions compared to the untreated areas. The reduction in the intensity of sunburn in the two treatment areas did not differ significantly. The investigators concluded that MPA

and HCB were safe and effective in the treatment in the sunburn in humans.

The basic form of benzocaine is bioactive and penetrates the damaged sunburned skin and limits the sensation of pain, burning, and itching. Among the benzocaine preparations that are commercially available, those consisting of 20% benzocaine base in propylene glycol are most effective. Relief is obtained for periods of 4–6 hours. The lack of efficacy of some of the manufactured preparations is most commonly related to insufficient concentrations of the active ingredient (less than 5% benzocaine).

Epidemiologic data on allergy, irritancy, and other reactions to benzocaine do not support the contention that it is a potent sensitizer. It has been, and is still, one of the safest topical anesthetic agents. Because it has a low degree of water solubility, the quantities of absorbed benzocaine are relatively insignificant, and plasma levels, which cause systemic reactions characterized by the soluble “caine” type drugs, are not evident with this drug. The convulsions and cardiac depression characteristic of the caine type drugs do not occur with this drug, and reports of such drug-related reactions are nonexistent. A 1% solution of lidocaine hydrochloride exaggerates rather than relieves the pain associated with sunburn.

More recently, we have been using a eutectic mixture of local anesthetic (EMLA) cream (Astra USA, Westborough, Massachusetts), composed of lidocaine 2.5% and prilocaine 2.5%. It is known to be an effective topical anesthetic agent. EMLA cream is noninvasive, easy to apply, widely available, and inexpensive. According to the manufacturers instructions, the onset of activity will take usually 1 hour.²³

VI.C. Delayed Reactions

The delayed sunlight/tissue interactions can be subdivided into two distinct groups: photocarcinogenesis and photoaging.

1. Photocarcinogenesis

Skin cancer is the most serious consequence of sunlight. Unfortunately, the UV spectrum for generation of skin cancer is still not adequately known. When the DNA in skin absorbs UV radiation directly, it leads to characteristic C-to-T and CC-to-TT mutations in p53 that seem to result in altered DNA.²⁴ Mutated p53 is identified in greater than 90% of the squamous cell carcinomas, 50% of basal cell carcinomas, and 60% of actinic keratoses.²⁵ UVB can produce squamous cell carcinoma in animals, as well as in human skin.²⁶ UVA can also promote squamous cell carcinoma in animals and human skin.²⁷

In the United States, many individuals are exposed to solar radiation in short bursts, which become cumulative over time. Exposure in this manner accounts for 80–90% of received UV radiation.²⁸ Melanoma is a leading cause of cancer death in the United States. The risk of dying of melanoma is 0.36% in white men and 0.21% in white women.²⁹ It is estimated that there will be more than one million new cases of basal cell and squamous cell carcinomas detected in 2003. Basal cell carcinomas occur more frequently in men and in three forms: nodular, morpheaform, and superficial. Squamous cell carcinoma, typically found on the face or other areas affected by chronic UV radiation, commonly presents as an erythematous papule, frequently with scales and superficial erosion. Typically, basal cell carcinomas remain localized and do not metastasize, while squamous cell carcinomas metastasize at a 5% rate.

Melanoma frequently occurs in individuals with history of intermittent but intense sun exposures. Four types of melanoma are known to exist: superficial spreading melanoma, nodular melanoma, lentigo melanoma, and acral-lentiginous melanoma. The two most common forms are the superficial spreading melanoma, which most frequently appears on the back and legs, and lentigo melanoma. The latter usually arises on chronically sun-exposed areas such as the face. If diagnosed early, surgical excision results in excellent prognosis, while a late

diagnosis requires treatment with chemotherapy, immunotherapy, or radiation.

2. Photoaging

Photoaging can occur in normal human skin exposed to UVA in the absence of UVB.³⁰ UVA I alone can produce photoaging.³¹ UVA causes the production of singlet oxygen that produces a cascade including transcription factors AP-I, AP-II, and NF kappa-B.³² It is important to emphasize that this cascade can be interrupted by antioxidants and retinoic acid.^{33,34}

Two thirds of UVA radiation reaching the surface of the earth consists of UVA I.³⁵ These rays penetrate far deeper into skin than UVB rays. Chronic UVA injury will result in photoaging. The epidermis absorbs primarily UVB rays that produce the most harmful effects for skin.²⁹ The damaging effects of acute exposure of UVB radiation include inflammation, sunburn, pigmentation changes, and skin hyperplasia. Exposure to UVB rays causes photoaging and immunosuppression, and in animal models has been shown to induce squamous cell carcinoma and melanoma.

UVA radiation is also associated with acute and chronic skin injury. The acute damage following exposure to UVA radiation produces erythema to a much lesser extent than UVB rays. In addition, UVA is the action spectrum for the vast majority of photoallergy and phototoxicity. Chronic exposure to UVA will cause photoaging, and in animal models, photocarcinogenesis. Repeated exposure to solar radiation, particularly for individuals with skin types I, II, and III who do not use sunscreens, can lead to aging of the skin. Lighter skin types allow the photons of UV radiation to penetrate deeper into the skin, causing more lasting damage, such as elastosis and eye damage.

Premature aging of the skin also results from prolonged exposure to the sun, which may damage both the epidermal and dermal layers of the skin. The epidermis becomes thickened and develops actinic keratoses. In the dermis, elastic tissues become a tangled shapeless mass without flexibility. Mature col-

lagen levels decrease, and the small blood vessels are dilated to an extreme. These effects lead to a leathery appearance of the skin. Areas protected from the sun, such as the buttocks, do not show these changes. Skin moisturizers and toners cannot reverse these signs of premature aging.

VII. SUNSCREEN

To reduce exposure to the sun's UV rays, The Skin Cancer Foundation, the American Academy of Dermatology, and the American Cancer Society have recommended sun protection practices that include the use of sunscreens.

VII.A. US Food and Drug Administration Sunscreen Regulations

The FDA regulates sunscreen products as over-the-counter (OTC) drugs. In 1999, the FDA issued a final rule in the form of a final monograph that established conditions under which OTC sunscreen drug products are generally recognized as safe and effective and not misbranded as part of the FDA's ongoing review of OTC drug products.³⁶ The FDA issued this final rule after reviewing public comments on the agency's proposed regulations, which was issued in the form of a tentative final monograph. Although this monograph was issued for implementation in December 2001, the full implementation date has been delayed until December 31, 2004. The 1999 regulations decreased the number of allowable sunscreen ingredients to 16 (Table 4).

The filters listed in Table 4 can be incorporated into sunscreen products, within the concentration specified for each ingredient, and the finished product provides a minimum SPF value of not less than 2 as measured by the FDA's testing procedure. Combinations of sunscreen active ingredients are used in sunscreen products. In the 1999 Final Monograph, the FDA indicated that two or more of the sunscreen active ingredients identified in Table 4 may be combined

TABLE 4. FDA Sunscreen Final Monograph³⁶

| Drug name | Concentration (%) | Absorbance |
|---|-------------------|-------------|
| Aminobenzoic acid | 15 | UVB |
| Avobenzene | 3 | UVA I |
| Cinoxate | 3 | UVB |
| Dioxybenzone | 3 | UVB, UVA II |
| Homosalate | 15 | UVB |
| Meradimate (menthyl anthranilate) | 5 | UVA II |
| Octocrylene | 10 | UVB |
| Octinoxate (octyl methoxycinnamate) | 7.5 | UVB |
| Octisalate (octylsalicylate) | 5 | UVB |
| Oxybenzone | 6 | UVB, UVA II |
| Padimate O | 8 | UVB |
| Ensulizole (phenylbenzimidazole sulphonic acid) | 4 | UVB |
| Sulisobenzene | 10 | UVB, UVA II |
| Titanium dioxide | 25 | Inorganic |
| Trolamine salicylate | 12 | UVB |
| Zinc oxide | 25 | Inorganic |

with each other in a single product when used in concentrations established for each ingredient. The concentration of each active ingredient must be sufficient to contribute to a minimum SPF of not less than 2 to the finished product. The finished product should have a minimum SPF of not less than the number of sunscreen active ingredients used in the combination, multiplied by two.

In addition to the statement of the sunscreen product identity, the FDA indicates that the following labeling statements must be prominently placed on the principal display panel. For products that satisfy the water-resistant product testing procedures, the manufacturer must insert one of the following terms: water, water/sweat, or water/perspiration resistant. For products that satisfy the very water-resistant sunscreen testing procedures, the manufacturer must select one of the following terms: very water resistant, very water/sweat resistant, or very water/perspiration resistant. For products that satisfy the water-resistant testing procedures, the manufacturer may state that

the product retains SPF after 40 minutes of activity in water, sweating, or perspiring. For products that satisfy the very water resistant testing procedures, the product must be labeled that it retains SPF after 80 minutes of activity in water, sweating, or perspiring. For more information on product labeling, refer to the appendix of the FDA monograph, which provides more detailed labeling instructions.

The Sun Protection Factor (SPF) of sunscreens is defined as the dose of UV radiation that will cause one minimal erythema dose (MED) on protected skin after application of 2 mg/cm² of sunscreen product divided by the UV radiation to produce one MED on unprotected skin. The amount of energy required to produce minimally perceptible redness in 24 hours is termed *MED*. To determine the SPF value for a specific sunscreen, volunteers with skin types I–III who are not taking medications known to produce abnormal sunlight responses or who do not have phototoxic or photoallergic responses, are exposed to radiation emitted by a solar simulator (290–400 nm). An area

between the beltline and shoulder blade of 50 cm² is marked off and application of sunscreen is 2 mg/cm². A waiting period of 15 minutes between application and exposure is allowed. The SPF is popularly interpreted as how much longer skin covered with sunscreen takes to burn compared with unprotected skin. A more accurate explanation of SPF is that it is the ratio of the least amount of UV energy that will produce minimal erythema on sunscreen protected skin to the amount of energy needed to produce the same erythema on unprotected skin.

In actual use, the SPF does not usually correlate with the SPF number on the label. It is essential that the appropriate amount of sunscreen be applied in actual use, the actual SPF is affected by a number of variables, including: the subject's skin type, sweating, water exposure, and most importantly, the amount of sunscreen applied and the frequency of the application. The thickness necessary to transmit only 10% incidence radiation is referred to as the *critical film thickness* and typically lies between 0.02 and 0.05 mm. The environment also plays a great role in the effectiveness of protection with factors such as humidity, altitude, and the degree of reflection off sand and snow.

Sunscreen products have a varying degree of substantivity or adherence to the skin after sweating, swimming, or washing. The FDA has outlined standardized tests that allow the manufacturer to appropriately label their sunscreen products. For products that satisfy the "very water resistant" sunscreen labeling, the sun protection value of the sunscreen must be determined after 80 minutes of water immersion using the following procedure: apply sunscreen product, followed by the waiting period after application of the sunscreen product indicated on the product labeling; 20 minutes of moderate activity in water; 20-minute rest period; 20 minutes' moderate activity in water; 20-minute rest period; 20 minutes' moderate activity in water; 20-minute rest period; 20 minutes' moderate activity in water; conclude test by air drying the test site, after which the standard solar simulator exposure is undertaken.

For manufacturers wanting to make the claim of "water resistant," the following water immersion

test must be followed: apply sunscreen product, followed by the waiting period after application of the sunscreen product indicated on the product labeling; 20 minutes of moderate activity in water; 20-minute rest period; 20 minutes' moderate activity in water; conclude water test by air drying test site, and begin solar simulator exposure to test site area. In both the evaluation of the "water resistant" or "very water resistant" sunscreen testing procedures, an indoor fresh water pool, whirlpool, and/or Jacuzzi maintained at 23–32°C must be used in these testing procedures. Fresh water is clean drinking water, and the pool and air temperature and the relative humidity must be recorded in these tests. The FDA monograph specified an upper limit of SPF 30, which means any product with an SPF greater than 30 can only be labeled as "SPF 30+." Newer product performance standards are listed in Table 5.

It is believed that an SPF 15 sunscreen provides excellent full UVB protection for healthy people. An SPF 15 product filters out more than 93% of UVB radiation, while an SPF 30 product filters out less than 97%. However, the product application technique outside of laboratories alters the SPF. As previously reported, the standard FDA testing method involves a sunscreen application of 2 mg/cm². In actual use, the average application thickness is closer to 0.5–1.0 mg/cm². Therefore, the difference of 4% between a SPF 15 and a SPF 30 sunscreen does have a noticeable effect in actual use.

Erythema, the key measurement in the SPF assay, is a relatively crude biologic endpoint. Consequently, it is not surprising that a comparison of an SPF 15 sunscreen vs. an SPF 30 sunscreen showed subclini-

TABLE 5. FDA Monograph Sunscreen Product Guide³⁶

| Sunburn protection | Sun protection facotrs |
|--------------------|------------------------|
| Minimal | 2–12 |
| Moderate | 12–30 |
| High | ≥30 |

cal damage—sunburn cell formation—in the former without visible erythema. The SPF 30 product provided significantly greater protection.

Although many sunscreens provide excellent UVB protection, they often lack UVA protection, particularly UVA I. With the availability of higher SPF products, which may encourage individuals to spend greater amounts of time in the sun without burning, concerns continue to be expressed about the adequacy of UVA protection of these products. Unfortunately, no consensus exists about the best method for measuring UVA protection. Recommendations generated by a consensus conference on this topic, organized by the American Academy of Dermatology, have been submitted to the FDA.³⁷

Sunscreen ingredients may be classified by dividing them into overall larger classes by their chemical structure. They also may be judged by their absorption spectrum.³⁸ It should be noted that sunscreen nomenclature can be confusing. Sunscreen filters can be identified by drug, chemical, or trade name; examples are listed in Table 6.

1. Chemical or Organic Sunscreens

The evolution of modern chemical or organic sunscreens is an elegant study of the use of structure/activity relationships to design new active ingredients

(Table 7). UVB organic (= chemical) sunscreen ingredients include aminobenzoic acid derivatives, anthranilates, benzophenones, octyl methoxycinnamate, octocrylene, octisalate, dibenzoylmethanes, and salicylates. Oxybenzone, menthyl anthranilate, and avobenzone are organic sunscreen ingredients that absorb primarily in the UVA range.

Aminobenzoic Acid Derivatives. PABA (λ_{max} , 283 nm) was one of the first chemical and organic sunscreens to be available. However, it had several problems associated with its use. Because PABA is water soluble, it was frequently used in alcoholic vehicles. These sunscreens stained clothing and were associated with many adverse skin reactions. Ester derivatives of PABA, predominantly octyl dimethyl PABA or padimate O, soon became more popular with greater compatibility in a variety of vehicles. Its use was associated with a lower potential for staining or adverse reactions. It is important to emphasize that the only aminobenzoic acid or derivative that provides complete UVB protection is roxadimate. Because of an increasing concern about the toxicity of this class of organic and chemical sunscreens, the use of this class of sunscreens has declined. Because of the scientists' need for sunscreens with higher SPF values, multiple active UVB sunscreens were incorporated into a single product to achieve the desired SPF, replacing single PABA esters.

TABLE 6. Sunscreen Nomenclature³⁶

| Over-the-counter drug | INCI ^a | Trade name |
|-----------------------|-----------------------------------|--------------------------------------|
| Avobenzone | Butyl methoxydibenzoylmethane | Parsol 1789 |
| Octinoxate | Octyl methoxycinnamate | Parsol MCX |
| Oxybenzone | Benzophenone-3 | Eusolex 4360, Uvinul M-40 |
| Padimate O | Octyldimethyl PABA | Escalol 507 |
| Z-COTE [®] | Transparent micro-fine zinc oxide | Z-COTE [®] HP1 ^b |
| T-COTE [®] | Titanium dioxide & dimethicone | T-COTE [®] 031 |

^a International Cosmetic Ingredient Dictionary and Handbook, ed 7. Washington DC, the Cosmetic, Toiletry and Fragrance Association, 1997.

^b Final over-the-counter drug products monograph on sunscreens. Fed Reg 1999; 64:27666–27798.

TABLE 7. Photoprotective Ingredients

| Organic Sunscreens | | Protection (nm) | UVB | UVAII | UVAI |
|---|-------------------------------------|-----------------|-----------|-----------|-----------|
| | | | (290–320) | (320–340) | (340–400) |
| Aminobenzoic acid and derivatives | | | | | |
| | PABA | 260–313 | partial | | |
| | Lisadimate (Glyceryl PABA) | 264–315 | partial | | |
| | Padimate O | 290–315 | partial | | |
| | Roxadimate | 280–330 | complete | partial | |
| Anthranilates | | | | | |
| | Menthyl anthranilate | 260–380 | complete | complete | partial |
| Benzophenones | | | | | |
| | Dioxybenzone | 250–390 | complete | complete | partial |
| | Oxybenzone | 270–350 | complete | complete | partial |
| | Sulisonbenzone (Eusolex 4360) | 260–375 | complete | complete | partial |
| Cinnamates | | | | | |
| | Octocrylene | 250–360 | complete | complete | partial |
| | Octyl methoxycinnamate (Parsol MCX) | 290–320 | complete | | |
| Dibenzoylmethanes | | | | | |
| | Avobenzene (Parsol 1789) | 320–400 | | complete | complete |
| Salicylates | | | | | |
| | Homosalate | 295–315 | partial | | |
| | Octyl salicylate | 280–320 | complete | | |
| | Trolamine salicylate | 260–320 | complete | | |
| Phenylbenzimidazole sulphonic acid | | | | | |
| | Ensilizoles | 290–340 | complete | complete | |
| Inorganic sunscreens | | | | | |
| | Titanium dioxide* | 290–700 | complete | complete | complete |
| | Zinc Oxide* | 290–700 | complete | complete | complete |

Key: partial = partial protection given in this UV range; complete = complete protection given in this UV range

* In non-micronized/non-microfined form

Anthranilates. Anthranilates have a broad spectrum of UV protection, with complete protection against UVB and UVA II, but only partial protections against UVA I. It is unfortunate that anthranilates are relatively weak UVB sunscreens, absorbing mainly in the UVA II spectrum. Because they are less effective sunscreens than benzophenones, their use has been limited. Another term for menthyl anthranilate is *meradimante*.

Benzophenones. Although benzophenones absorb most efficiently in the UVB range, the UV absorption extends well into the UV AII range, with two significant absorption peaks (λ_{\max} , 288 and 325 nm). Consequently, these sunscreens are used primarily as UVA absorbers but boost SPF levels when used in combination with other UVB absorbers. Oxybenzone is the most frequently used benzophenone.

Octyl methoxycinnamate. Cinnamates are the most potent UVB sunscreens and have largely replaced PABA derivatives. Octinoxate (octyl methoxycinnamate) is the most frequently used sunscreen ingredient. In order of magnitude, octinoxate is less potent than padimate O and requires additional UVB absorbers to achieve higher SPF levels in a final product.

Octocrylene. Octocrylene may be used in combination with other UV absorbers to achieve higher SPF formulas. Octocrylene may also be used with other sunscreen ingredients, such as avobenzone, to add to the overall stability of these ingredients in a specific formula.

Avobenzone. Avobenzone, also known as Parsol 1789, is chemically known as butyl methoxydibenzoylmethane. It has been approved by the FDA for OTC use in the United States. Its use in Europe as a sunscreen occurred prior to its introduction into the United States. Because its spectrum of activity is restricted to UV AI and UV AII, it must be used in combination with sunscreens that are effective against UVB. Concerns have been raised about its photostability and its potential to degrade other sunscreen ingredients in products in which it is used. In a review of contact and photocontact sensitivity to sunscreens in 1997, Schauder and Ippen³⁹ reported that an isolated allergy to avobenzone was rare.

Octisalate. Octisalate or octyl salicylate has a spectrum of activity predominantly in the UVB range. Because they are relatively weak UVB absorbers, their use has been supplanted by the more efficient PABA derivatives and cinnamate derivatives. However, they may be used occasionally to augment other UVB absorbers. Salicylates have an excellent safety record with an additional ability to solubilize other sunscreen ingredients, including oxybenzone and avobenzone. With an interest in reaching higher SPF levels, more octyl salicylates are being used followed by homosalates.

Ensulizole (Phenylbenzimidazole sulfonic acid). Most

organic sunscreen ingredients are oils that are soluble in the oil phase of emulsion systems, accounting, in part, for the heavy, greasy aesthetics of many of these products. In contrast, phenylbenzimidazole sulfonic acid is primarily a water-soluble UVB sunscreen that can be used in the water phase in the emulsion systems. It is a selective UVB filter, allowing almost all UVA transmission. Because of its water solubility, it results in an aesthetically pleasing formulation that includes daily use moisturizer-containing sunscreen. The oil-soluble sunscreens have a tendency to be greasy and soil clothes. Because it is water soluble, it is often used in clear gels. This sunscreen boosts the SPF of other organic and inorganic sunscreens.

2. Nonchemical or Inorganic Sunscreens

Inorganic sunscreens used to be referred to as *non-chemical sunscreens*; they include two agents: titanium dioxide and zinc oxide. These agents are manufactured in submicroscopic size (<200 nm) so that visible light scattering is minimized and the particles appear invisible on the skin. At small particle size, the particles attenuate UV light, primarily by absorption similar to an organic sunscreen. No irritant or sensitization reactions have been noted with either agent. Zinc oxide is a category I FDA-approved skin protectant. In addition, it has been approved for use in the treatment of diaper rash because it is safe to apply to inflamed nonintact skin.

Modest crystal surface photosensitivity resulting in free-radical generation has been demonstrated with titanium dioxide. Coating the titanium crystal with silica or dimethicone dramatically reduces this photosensitivity.⁴⁰ Modest crystal surface photosensitivity has not been encountered with zinc oxide. At higher concentrations, inorganic sunscreens agglomerate and develop a white appearance. Zinc oxide is less whitening in this form than titanium dioxide. Consequently, good formulation technology is essential to limit agglomeration.

In micronized form, titanium dioxide and zinc oxide protect mainly against UV light from 250–340

nm. However, it is important to point out that protection against UVAI is superior for zinc oxide.

VII.B. Vehicles

The vehicle type is very important in determining sunscreen efficacy and aesthetics. Ingredients such as solvents and emollients can have considerable influence on the magnitude of UV absorbance by the active ingredients and which wavelengths they absorb.⁴¹ The nature of the film formed on the skin surface is considerably influenced by the film formers and emulsifiers. High SPF products require that the ingredients provide a uniform and thick sunscreen film with minimum interaction of inert ingredients with active ingredients.³⁸ The water resistance and durability of the product are dependant upon the components of the vehicle.

Lotions and creams are the most popular sunscreen vehicles. Because they allow the widest variety in formulation, two-phase oil-in-water or water-in-oil emulsion is the most popular. Because most sunscreen ingredients are lipid soluble, they are incorporated into the oil phase of the emulsion. Sunscreen products with high SPF may contain 20–40% sunscreen oils, accounting for their greasy feel. Foams and dry lotions, often available as “sport lotions,” represent the manufacturer’s efforts to produce a less greasy product. Sticks easily incorporate lipid-soluble sunscreens, which are thickened with waxes and petrolatum and are heavier on application, but are useful for protecting limited areas, such as lips, nose, or around the eyes. Aerosols result in a dispersed film but are easy to apply.

Sunscreens have been integrated into a broader range of consumer products, including daily-use cosmetics. Consequently, the FDA monograph distinguishes between beach and non-beach products. Because of more awareness of sunscreens in general, they are now being used all year, not just in the summer. Moisturizers that incorporate sunscreen are usually oil-in-water emulsions. Water-soluble sunscreen ingredients are frequently used to reduce

the oil phase and to enhance the cosmetic elegance. Foundation makeup without sunscreen often has an SPF of 3 to 4 because of its pigment content. When inorganic sunscreen particulates—titanium dioxide and zinc oxide—are added to these foundations, higher SPF can be achieved with or without the use of organic or chemical sunscreen. Makeup with sunscreen has intrinsic full-spectrum UVA protection due to opacity.

Lipsticks frequently add organic sunscreen to provide enhanced SPF protection. The use of lipstick has been shown to contribute to a lower incidence of lip cancer in women.⁴² More recently, organic sunscreens have been added to lipsticks to enhance its SPF protection.

VII.C. Photostability

Inorganic sunscreen ingredients are photostable and remain intact after irradiation. Photolability has been reported with some organic sunscreens to include octinoxate (octylmethoxycinnamates and Padimate O). In contrast, oxybenzone has been reported to be relatively stable.⁴³ Photolability has also been encountered with avobenzone.⁴⁴

VII.D. Preservatives

In order to assure photostability of chemical sunscreens, preservatives are added to most sunscreen products. These preservatives can lengthen the shelf life of sunscreen products after manufacture. However, because they are biologically reactive substances, most preservatives have allergenic potential, which can result in contact dermatitis and other skin inflammations.⁴⁵ Several preservatives used in sunscreen products include chloromethylisothiazolinone, butyl carbonate, diazolidinyl urea (DU), and various parabens. Parabens methyl-, ethyl-, propyl-, benzyl-, and butyl- are the most common preservatives used in pharmaceutical, cosmetic, and food industries. They

are relatively nonirritating and nontoxic, especially given their widespread use, and they also provide excellent antimicrobial coverage in sunscreen products. Parabens are the alkyl esters of *p*-hydroxybenzoic acid.⁴⁶ DU is a relatively gentle preservative on its own but causes more sensitization as a formaldehyde releasing agent, which is how it is currently used in cosmetics and personal-care products.⁴⁷ However, sunscreen creams have had more success with the use of DU as a preservative.⁴⁸

VII.E. Phototoxicity

Subjective irritation associated with burning or stinging is the most common sensitivity complaint about sunscreen. This irritation is most commonly observed around the eyes. Persistent objective irritant contact dermatitis is infrequent and is difficult to distinguish from true allergic contact dermatitis. Fragrances, preservatives, and other excipients account for many of the allergic reactions that occur with sunscreens. Reports in the literature of sensitization associated with many commonly used sunscreen agents, including *p*-aminobenzoic acid, PABA derivatives, anthranilates, salicylates, cinnamates, benzophenones, and dibenzolmethane derivatives have been reported.⁴⁹ Several of the case reports involve subjects with various photodermatoses, implicating a sensitivity of the patients' skin to both light and chemicals. Despite the widespread use of sunscreen, the small number of published reports of contact and photocontact sensitization of these agents suggest that sensitization is either less than commonly perceived or underreported.

On the basis of these investigations, The Skin Cancer Foundation and the American Academy of Dermatology recommend that a broad-spectrum sunscreen with an SPF of at least 15 be used every day. The sunscreen should be applied 15–30 minutes before going outdoors and reapplied every 2 hours or after exposure to water. To protect against UVAI radiation, select a sunscreen formula that contains

either avobenzene or zinc oxide.⁵⁰ When going to the beach, it is advisable to use a sunscreen that is labeled as “very water resistant.”

VIII. TOPICAL ANTIOXIDANTS

The skin uses antioxidants to protect itself from the sunlight. The antioxidants neutralize the harmful chemical reactions that lead to skin damage. The major nonenzymatic antioxidants used by the skin to reduce photodamage are vitamin C (L-ascorbic acid) in the aqueous phase, vitamin E (α -tocopherol), and ubiquinol 10 in the lipid phase, glutathione intracellularly, and α -lipoic acid in the mitochondria. When compared on a molar basis, the activity of vitamin C is more than 10-fold greater than that of all other antioxidants.⁵¹

Investigations have demonstrated that antioxidants can be delivered into skin percutaneously to provide photoprotection. The beneficial photoprotective effects have been shown for vitamin C,⁵² vitamin E,^{53,54} and α -lipoic acid.⁵⁵ Vitamin C has been shown to reduce inflammation following sunburn in human skin, be protective after sun exposure, and prevent UV light immunosuppression.

Divalent zinc ion has been shown to have antioxidant properties in cellular systems^{56,57} and in vivo.⁵⁸ Although it is effective topically, its mechanism of action is still not known.⁵⁹

IX. SYSTEMIC ANTIOXIDANTS

Several observations suggest that systemic photoprotection may be possible. *Polypodium leucotomos* has been used successfully to treat inflammatory diseases.⁶⁰ Oral and topical *Polypodium leucotomos* has demonstrated photoprotection as measured by an associated increased MED and minimal phototoxic dose. In addition, beta carotene has been used to diminish photosensitivity in patients with erythropoietic protoporphyria. Antimalarials have also been shown to reduce photosensitiv-

ity in polymorphous light reaction, cutaneous lupus erythematosus, and solar urticaria.

Antioxidants, such as ascorbic acid and D- α -tocopherol, have been found to be photoprotective in some in vitro studies and animal experiments. In an investigation reported by Eberlein-König et al.,⁶¹ these clinicians assessed the protective effect of systemic vitamins C and E against sunburn in humans. In a double-blind placebo-control study, each of 10 subjects took daily either 2 gm of L-ascorbic acid (ASC) combined with 1000 IU of D- α -tocopherol (α -Toc) or placebo. The sunburn reaction before and after 8 days of therapy was measured by determining the MED and by recording the blood flow of skin exposed to incremental UV doses against that of non-irradiated skin. This combination of vitamins C and E decreased significantly the sunburn reaction.

In another clinical study, Fuchs and Kern⁶² also determined whether oral supplementation with α -Toc, ASC, or α -Toc combined with ASC influence the solar simulated radiation induced skin inflammation in healthy volunteers. They investigated in a prospective, randomized, and placebo-controlled study the following treatment groups: group 1: α -Toc, 2 g/day; group 2: ASC 3 g/day; group 3: α -Toc 2 g/day combined with ASC 3 g/day; and group 4: placebo. Before and 50 days after supplementation, they analyzed α -Toc and ASC concentrations in keratinocytes. The dose response curve of UV erythema was measured by reflectance spectrophotometry with UVB exposure of 310 nm and the MED by visual grading before and after supplementation. Fifty days after supplementation, α -Toc keratinocyte levels were increased in groups 1 and 3. In addition, ASC concentrations were increased in groups 2 and 3. Finally, the α/γ -Toc ratio increased in groups 1 and 3. The dose response curve of UV-induced erythema showed a significant flattening, and the MED increased from 103 ± 29 mJ/cm² (before supplementation) to 183 ± 35 mJ/cm² (after supplementation) in group 3, while there were no significant changes in groups 1 and 2 after vitamin supplementation. The investigators concluded that α -Toc and ASC acted synergistically in the suppression of the sunburn reaction.

X. PHOTOTOXIC AND PHOTOALLERGIC REACTIONS

Adverse photosensitivity reactions may be either phototoxic or photoallergic, which can occur following either the topical application or parenteral administration of certain drugs or chemicals.¹⁵ Abnormal reactions occur in skin sites predominantly exposed to sunlight to include the face, ears, back of the neck, "V" of the neck, and extensor surfaces of the arms and hands. Phototoxic reactions can be elicited in any normal healthy individual when appropriate concentrations of an offending agent are either applied topically (contact) or given orally (systemic) (Table 8). After exposure to light, the agent leads to a sunburn reaction that occurs 5–18 hours after exposure to the sun and is usually maximum at 36–72 hours. Desquamation, hyperpigmentation, or hypopigmentation may also occur.

Furocoumarins, encountered in Persian lime juice or in cosmetic agents containing plant extracts or other essential oils, frequently produce phototoxic reactions that are manifested clinically by hyperpigmentation confined to the anatomic site where the agent is applied. Systemic phototoxic agents will induce a photosensitivity response in all individuals, provided an adequate dose of radiation in the action spectral range of that particular photosensitizer is delivered. The reaction occurs within minutes to hours upon exposure to sunlight following the oral or parenteral administration of a variety of different drugs.

The photoallergic reaction is a cell-mediated immune response that may develop in immunological sensitized individuals. The absorbed light promotes a photochemical reaction between the drug and skin protein. The drug acts to form a haptenic group and either combines directly with the protein to form a photoantigen or is altered by the absorbed energy, after which it reacts with the protein to form an antigen. All first allergic reactions include a latent period of at least 10 days before the allergic reaction occurs. After that, under the same conditions of the photosensitizing chemical interacting with sunlight, the interval between the time of contact with the

TABLE 8. Examples of Photosensitizers

| Systemic photosensitizers | Topical photosensitizers |
|---------------------------------|---|
| Sulfonamides | Plants: Ragweed and furocoumarins (i.e., figs, limes, etc.) |
| Chlorothiazides, phenothiazides | Drugs: Sulfa, tar |
| Antibiotics | Dyes: Rose Bengal, fluorescein Cosmetics: Furocoumarin compounds (i.e, oil of lime and oil of Bergamot) Sunscreens ⁶³ : PABA, Oxybenzone, Eusolex 8020, isopropyl dibenzoylmethane, Glyceryl PABA, Parsol 1789, Eusolex 6300 3-(4'-methyl-benzylidene) camphor, Padimate A, Padimate O, GivTan F 2-ethoxyethyl- <i>p</i> -methoxycinnamate, Mexenone, Eusolex 232 2-phenyl-benzimidazole-5-sulfonic acid, Sulisonbenzone, Benzyl salicylate, Parsol MCX 2-ethylhexyl- <i>p</i> -methoxycinnamate, Benzophenone (NOS), Dioxybenzone, Witisol, Borneolone, Digalloyl trioleate |

sensitizing agent and the allergic reaction is within 24 hours. Close examination of the skin reaction shows that it differs from sunburn, usually manifesting as eczematous dermatitis. In sensitized individuals, much smaller quantities of chemical sensitizers are capable of reproducing the photoallergic effect than phototoxic reactions. Common photoallergic agents are halogenated salicylanilides, phenols, and carbanilides.

In some patients, extreme photosensitivity could persist for years. This condition, known as *chronic actinic dermatitis*, could start as photoallergy; however, it could also arise de novo. These patients will often display thickened, hyperpigmented, and hypopigmented skin with fissuring.

X.A. Treatment

Therapy of acute phototoxic reactions, induced by a topical or systemic agent, consists of removing the agent and avoiding exposure to the sun. Clinical phototesting (i.e., the determination of the MED) can aid in making the diagnosis. In theory, any lesion in which sunlight plays an etiologic role should be reproducible using artificial light sources and the offending agent. However, because of the potential severe bullous eruption on phototesting using known

phototoxic agents, such testing is not recommended. Topical corticosteroids, such as 0.1% triamcinolone cream or ointment, two or three times a day are usually adequate to relieve skin reactions. It is important to avoid persistent or repeated use of the more potent topical corticosteroids, such as fluocinonide and fluocinolone acetonide, when areas such as the face are involved, because prolonged use can lead to skin atrophy and striae. When photosensitive reactions are severe, a 7- to 10-day tapering course of oral prednisone, starting with 40–60 mg orally on the first day, is often beneficial.

Antihistamines suppress symptoms in some patients with photoallergic reactions. In most patients, the eruption associated with chemical photosensitivity subsides within a week or two of avoiding the chemical and sunlight. Exposure to sun should be avoided. When exposure is unavoidable, broad-spectrum sunscreens with a high SPF should be used.

X.B. Other Photodermatoses

Certain diseases are aggravated or induced by sunlight. The example of photosensitivity induced by endogenous agents is the cutaneous porphyrias.⁶⁴ In these diseases, the photosensitivity is due to the overproduction of phototoxic porphyrins. The wave-

lengths for elicitation of cutaneous reactions are mainly in the visible-light spectrum (4000–7000 Å) and correspond to the rays that are strongly absorbed by porphyrin in vitro (4000–4100 Å, known as the *Soret band*). Skin fragility, vesiculobullous, urticarial, or eczematous reactions are seen in different types of porphyria. Milia and pigmentary changes may also be present in these reactions. The most mutilating type of porphyrias is congenital erythropoietic porphyria (CEP), also known as Günther's disease.⁶⁵ Congenital erythropoietic porphyria is characterized by several skin-mutilating effects, such as vesicles and bullae, which lead to scarring. These dramatic effects are only seen upon cutaneous exposure to the sun. Another type of porphyria, erythropoietic protoporphyria is a disease distinguished by the lack of an enzyme necessary to catalyze the incorporation of iron into protoporphyrin, which manifests itself as a stinging sensation upon exposure to sunlight; this is much more common than CEP. Symptoms and signs of this sensitivity to sunlight start in childhood. The adverse reactions to sunlight in most patients with erythropoietic protoporphyria can be minimized by the oral ingestion of β -carotene.

The mechanism of light-induced reactions in the rare genetic disease xeroderma pigmentosum has also been elucidated.⁶⁶ This disorder is due to ineffective excision or post-replication repair of DNA following exposure to UV radiation. Patients with xeroderma pigmentosum exhibit extreme sun sensitivity by age 1 and generally develop skin cancer by age 8.

Certain other diseases predispose patients to increased sensitivity to sunlight, but the mechanism in most of these disorders is unknown. Sun sensitivity in collagen-vascular diseases is well known. Sixty to seventy percent of patients with systemic lupus erythematosus (SLE) are photosensitive.⁶⁷ Both UVA and UVB have been implicated in inducing lesions in patients with SLE.

Polymorphous light eruption (PLE) presents as erythematous, macular, sometimes urticarial eruption that develops in the sun-exposed area within 24 hours after exposure; it usually starts in the spring.⁶⁸ It may

be pruritic and typically lasts through the summer into the fall, eventually disappearing in the winter, only to recur the following spring. There are usually no associated systemic symptoms.

Other photoaggravated disorders include phenylketonuria and pellagra. Diseases that are exacerbated on exposure to the sun include herpes simplex, varicella, lymphogranuloma venereum, and some dermatologic disorders (e.g., psoriasis, lichen planus, pityriasis rubra pilaris, pemphigus erythematosus, and erythema multiforme).

XI. BENEFICIAL EFFECTS OF UV RADIATION

Heretofore, this collective review has focused on the damaging effects of UV radiation. Consequently, it is important to emphasize that UV radiation provides both physiological and psychological benefits to humans. For example, the multiple psychological stresses that have been documented in night-time workers, jet-lagged passengers, and long-term travelers in submarines have been corrected by exposure to a lit environment.⁶⁹ In addition, appropriate exposure to UV light ensures appropriate vitamin D production, which maintains proper calcium metabolism and appropriate bone formation. In the absence of UV, there is inadequate vitamin D production with interruption of calcium metabolism and bone formation. However, it should be noted that the regular diet does contain an adequate amount of vitamin D; it has been shown that patients with xeroderma pigmentosum, who are very well protected from sunlight, do have plasma vitamin D levels within the normal range. Moreover, circadian and biological rhythms, such as reproduction, are also influenced by UV light. Without UV-stimulated secretion of melatonin from the pineal gland, there will be inadequate functioning of the sex organs.⁷⁰ UV light, as well as visible light, has been used to treat hyperbilirubinemia of prematurity and prevent the damaging effects of kernicterus, or accumulation of bilirubin in the brain.⁷¹

XII. CONSUMER EDUCATION

The Skin Cancer Foundation is the only national and international foundation concerned exclusively with skin cancers. Their mission is to stem the epidemic of skin cancer with preventative public education campaigns to teach adults, children, and their caregivers about the dangerous UV rays of the sun as well as change public attitudes and behavior toward tanning and sun exposure. The Foundation encourages detection of skin cancers at the earliest stage, when they are almost always curable; offers physician education and training programs; and supports research into effective new skin cancer diagnostic techniques and therapies. Since 1981, The Foundation has offered a Seal of Recommendation for photoprotective products that reinforce the Foundation's educational guidelines and advocacy of the use of UV-protective products. Photoprotective product categories include not only sunscreens, but also sunglasses, window films, laundry detergent additives, and photoprotective fabrics, including clothing. More than 200 products in the United States and some 60 abroad currently have been awarded the Seal.

In order to be certified, the product must have a minimum SPF/UPF of 15 and meet the specified criteria of The Skin Cancer Foundation's Photobiology Committee. These include stringent testing to support the SPF/UPF value and verify certain safety requirements, such as phototoxicity and contact irritancy. If water resistance claims are made, the product must be tested to ascertain its potency after repeated immersion. The Skin Cancer Foundation performs a valuable service to the industry and to the consumer by ensuring a product's ongoing adherence to FDA guidelines.

The scientific literature is filled with scientific studies that confirm that the consumer must be carefully and accurately informed about the appropriate use of sunscreens as well as the dangers of failing to comply with the recommendations for appropriate sunscreen use.

In 1999, Emmons and Colditz⁷² wrote a compel-

ling editorial to develop a national policy that would prevent excess sun exposure. They pointed out that there is strong evidence to indicate that childhood sun exposure is an important risk factor for melanoma. The seminal observation linking age at exposure to risk was the finding that the incidence of melanoma increased among people who had migrated from northern latitudes to more equatorial latitudes, but only among the immigrants who were children at the time of the migration. They concluded that reduction of exposure to the sun throughout life is warranted to reduce the risk of melanoma and non-melanoma skin cancer.

In other parts of the world, they pointed out that sun protection is viewed as a societal responsibility. In these countries, they have established strong norms that encourage citizens to use a variety of sun protection strategies. For example, Australia's "Slip, Slop, Slap" campaign is a challenge to children and adults to "slip on a long sleeve shirt, slop on some SPF 15+ sunscreen, and slap on a broad-brim hat." In addition, schools in Australia have "no hat-no play" policies that restrict children who do not have hats from playing outdoors. The Skin Cancer Foundation has played a major role in effecting awareness and change in the United States.

Wright et al.⁷³ highlighted some of the mechanisms of sunscreen failure. In their study, they interviewed 67 adults at a public beach in Galveston, Texas, over a 4th of July weekend, about their sun-related activities and habits. Each person participating in the study was asked a series of questions that included his or her use of sunscreen and other sun protective items such as hats, clothing, and sunglasses; parts of the body to which sunscreen was applied; number of times previously sunburned; number of hours spent at the beach; and how often sunscreen was applied throughout the day. Their study found that 73% of those that applied sunscreen became sunburned. They found that the majority of these people went swimming and did not reapply sunscreen afterward. They noted that all of the beachgoers that did not get sunburned reapplied sunscreen every 1-2 hours

TABLE 9. Guidelines for Sunscreen Use

- Wear a broad-spectrum, "water resistant" sunscreen with an SPF of 15+.
- Use sunscreens every day whenever you are outdoors, even if you will be in your automobile.
- Apply sunscreens to dry skin 15–30 minutes BEFORE going outdoors.
- Remember to apply sunscreen to the ears, neck, top of head (if bald or have thinning hair), tops of feet, and behind the knees.
- One ounce of sunscreen, the size of a golf ball or shot glass, is considered the amount needed to cover the exposed areas of the body completely.
- REAPPLY sunscreens every 2 hours or immediately after swimming or strenuous activity, even if you are using a "very water resistant" sunscreen.
- Avoid deliberate tanning, seek the shade, wear sun-protective clothing, and limit exposure during peak hours.

and after leaving the water if they went swimming. In general, they reported that even swimmers who used sunscreen were significantly more likely to be sunburned than nonswimming sunscreen users. Among sunscreen users, they found that those who applied sunscreen felt that one application of sunscreen would work 3 hours without reapplying. Other sunscreen users believed a single application would last at least 4 hours.

They emphasized that it has been well documented that people who wait more than 2.5 hours to reapply their sunscreens have five times more chance of getting sunburned than those who reapply sunscreen every two hours. In addition, they pointed out that it has been well documented that sunscreen users do not apply enough sunscreen in a single application to protect adequately the whole body. They indicated that one ounce of sunscreen, enough to fill a shot glass, or the size of a golf ball, is considered the amount needed to cover the exposed areas of the body completely.

Taylor and Diffey⁷⁴ devised a simple dosage guide for sunscreen that should help the consumers. Their dosage guide was based on a "rule of nines" that divides the body's surface area into 11 areas, each representing 9% of the total body. These areas are: (1) head, neck, and face; (2) left arm; (3) right arm; (4) upper back; (5) lower back; (6) upper front torso; (7) lower front torso; (8) right upper leg and thigh; (9) left upper leg and thigh; (10) left lower leg and foot; and (11) right lower leg and foot. The clinicians indicate that consumers are unlikely to cover themselves or their families with such a copious layer of sunscreen and would rather apply

half this amount. A less daunting proposition offered by the clinicians was to apply one finger of sunscreen, with the understanding that the resultant protection would be only about half that stated on the product. They encouraged the consumer to reapply one finger's worth of sunscreen within half an hour of the initial application in order to achieve optimal application.

On the basis of this extensive collective review of the scientific basis for the use of sunscreens, we have outlined a series of recommendations regarding the use of sunscreens that are illustrated in Table 9. This table can be easily downloaded by office personnel to be given out as handouts to their patients to encourage all of their patients to gain the excellent photoprotective effects of sunscreen.

XIII. CONCLUSION

Skin cancer is the most common cancer diagnosed in the United States, and its incidence continues to rise. Epidemiological studies have documented that excessive sun exposure increases the risk of developing skin cancer. Consequently, it is mandatory that the skin be protected from damage that occurs from UV exposure. It is the purpose of this report to review the scientific basis for photoprotection by sunscreens, topical antioxidants, and systemic antioxidants to reduce sun exposure. The US Food and Drug Administration regulates sunscreen products as over-the-counter drugs. Sunscreens are organic UV absorbers and inorganic UV absorbers. Other important sunscreen con-

siderations include the sunscreen vehicle, sunscreen photostability, sunscreen preservatives, and sunscreen photoallergy and phototoxicity. Topical and systemic antioxidants have now been shown to supplement the photoprotective effects of sunscreen. The Skin Cancer Foundation, the only national and international non-profit organization concerned exclusively with cancer of the skin, is playing a leadership role in eliminating skin cancer in our world.

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DEDICATION

This article is dedicated to the many survivors of and those battling with cancer, as well as their families, loved ones, and caregivers. After their heroic experiences, we would all agree that the best treatment for skin cancer is prevention, which is one of the major objectives of The Skin Cancer Foundation. We must acknowledge the gifted Manager of Corporate Programs, Sabrina Valvo, for her dedication and tireless efforts to make these scientific articles on skin cancer prevention possible.

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