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Shedding Light on
Complete UV Protection



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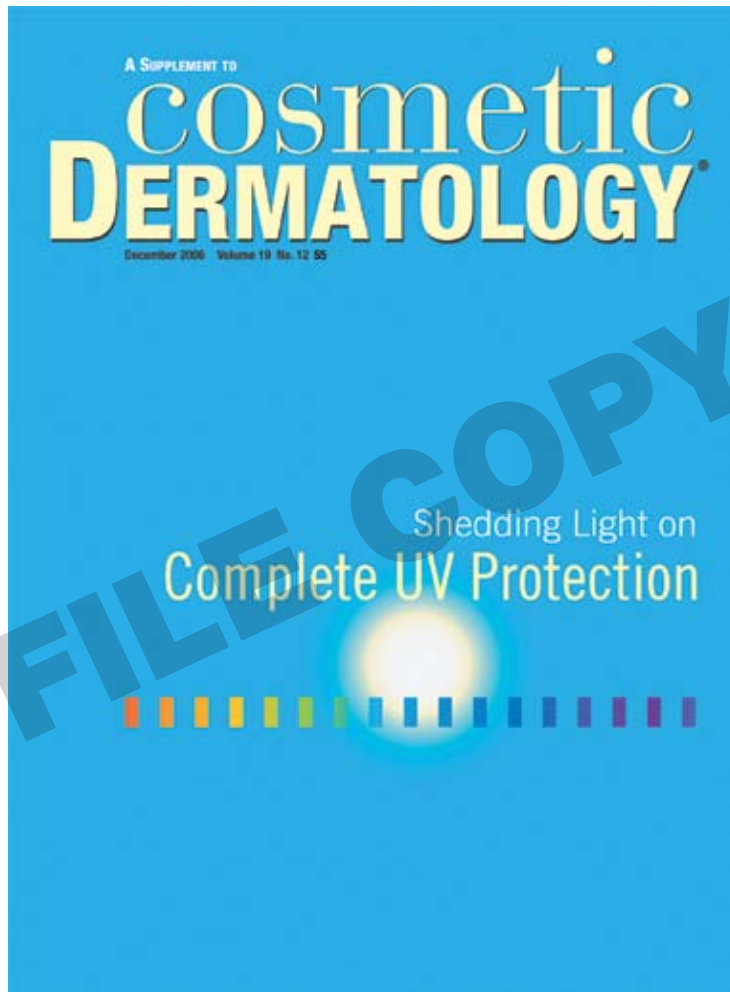
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Shedding Light on Complete UV Protection

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Broad-spectrum photoprotection, which is necessary to prevent skin cancer, photoaging, and other dermatologic diseases, shields the skin from the entire range of solar UV radiation. Although many sunscreens effectively protect against UVB radiation, few are capable of filtering out most UVA radiation, and uniform standards are lacking for assessing how well sunscreens protect against UVA rays. This supplement describes the damaging effects of UVA radiation, reviews currently available UVA-testing methodologies and sunscreen filter technology, and describes ecamsule (Mexoryl™ SX), a newly approved UVA filter that, in combination with other UV filters, provides improved UVA and UVB photoprotection.

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Sunscreens have been commercially available since the late 1920s. In 1972, the Food and Drug Administration (FDA) reclassified sunscreens as over-the-counter (OTC) drugs, and this is how all sunscreen UV filters continue to be regulated in the United States. In 1978, *The Federal Register* published guidelines on sunscreens, which were followed by an educational campaign in the 1980s that ultimately led to high public acceptance of sun protection factor (SPF) labeling. SPF was based on the known photochemical effects of UVB radiation (290–320 nm). However, our understanding of the effects of UV exposure has increased dramatically in recent years, and growing evidence suggests that the effects of UVA radiation (320–400 nm) are more significant in long-term skin damage than acute UVB effects, such as erythema.¹

FDA SUNSCREEN MONOGRAPH

In 1999, the FDA finalized its OTC drug products monograph on sunscreens,² which established guidelines for the safety, efficacy, and labeling of these products. These guidelines define SPF as the dose of UV radiation (UVR) required to produce 1 minimal erythema dose on skin protected with an application of 2 mg/cm² of filter divided by the UVR required to produce 1 minimal erythema dose on unprotected skin. However, several studies have indicated that in real-world conditions, the median thickness of the applied product is actually in the range of 0.5 to 1.2 mg/cm², which lowers the effectiveness of the sunscreen product significantly.^{3–5} Furthermore, SPF testing is designed to measure UVB protection, which does not necessarily correlate with the degree of UVA protection found in sunscreens.

CURRENT STATE OF SUNSCREEN COMPOSITION AND ASSESSMENT

The contribution of UVA exposure to skin cancer has become more fully appreciated in recent years, and there is increasing indirect evidence that other long-term photoaging effects that occur to sunscreen-protected skin are attributable to the UVA portion of the UV

BROAD-SPECTRUM UV PROTECTION

spectrum. This is evidenced by a common complaint from dermatology patients that they tan even though they use sunscreen, which is due to the sunscreen formulation containing either UVA filters with inadequate absorption in the UVA range or filters with inadequate photostability. The latter would require frequent reapplication of the sunscreen to ensure continuous protection. Unfortunately, there is not a single effective method for evaluating the efficacy of sunscreens against UVA rays.

SUN PROTECTION STRATEGIES AND NEW UVA FILTER TECHNOLOGY

The Environment Council of the American Academy of Dermatology (AAD) recommends that in addition to sun avoidance and minimizing exposure during peak UVR hours (10 AM–4 PM), appropriate clothing, wide-brimmed hats, sunglasses, and broad-spectrum sunscreen be used to achieve optimal photoprotection.⁶ Recently, an important gap in sunscreen filter technology has been filled with the FDA approval of ecamsule (Mexoryl™ SX), a photostable, water-soluble organic filter designed to protect the skin from harmful short-wavelength (320–340 nm) UVA radiation. When combined with octocrylene, a UVB protectant, and avobenzone, an octocrylene-stabilized long-wavelength (340–400 nm) UVA protectant, ecamsule offers complete broad-spectrum UVA and UVB protection.

EFFECTS OF UVA AND UVB ON THE SKIN

Exposure to UVR has numerous acute, chronic, or delayed negative effects on the skin, including erythema, photoaging, immuno-suppression, mutagenicity, and carcinogenicity. Similar to short-wavelength UVB, the contributions of UVA to skin cancer formation are mediated through its ability to damage DNA. UVB radiation can effectively induce DNA photoproducts in all layers of the epidermis and affect DNA directly, primarily by generating highly mutagenic cyclobutane-type pyrimidine dimers and pyrimidine-pyrimidone (6-4) photoproducts. The mutagenic effects of these lesions are counteracted by activation of p53 in response to UVB. Loss of p53 function results in a UV-mutator phenotype that is central in the genesis of squamous cell carcinoma⁷; it is found in more than 90% of squamous cell carcinomas and in most basal cell

carcinomas and actinic keratoses.⁸

UVA is capable of only weak excitation of the DNA molecule and subsequent formation of DNA photoproducts. Indirect effects on DNA, mediated through excitation of other cellular molecules and formation of reactive oxygen species, have long been thought to mediate the mutagenic potential of UVA.⁹ Recently, however, it has been shown that UVA-induced mutations are also mediated by DNA photoproducts.¹⁰ A higher mutagenic potential of UVA-induced DNA photoproducts, as compared to UVB-induced products, is thought to be due to a protective DNA damage response with UVA (eg, as seen by a less prominent p53 activation).¹⁰

RELATIVE CONTRIBUTION OF UVA AND UVB TO PHOTOCARCINOGENESIS

When evaluating the contributions of UVA and UVB radiation to solar photocarcinogenesis, it is important to consider that UVA is far more abundant than UVB. Although exact data are missing, several lines of evidence from animal models suggest that both UVA and UVB contribute to nonmelanoma skin cancer and melanoma formation.^{9,11} This underlines the urgent need to better ensure that sunscreen products include effective UVA filters.

UVA AND PHOTOAGING

Photoaging is characterized by alterations to many aspects of the skin and its functions, including wrinkles, roughness, lack of elasticity, dyspigmentation or hyperpigmentation spots, and a variety of benign or malignant tumors. Disorganization,

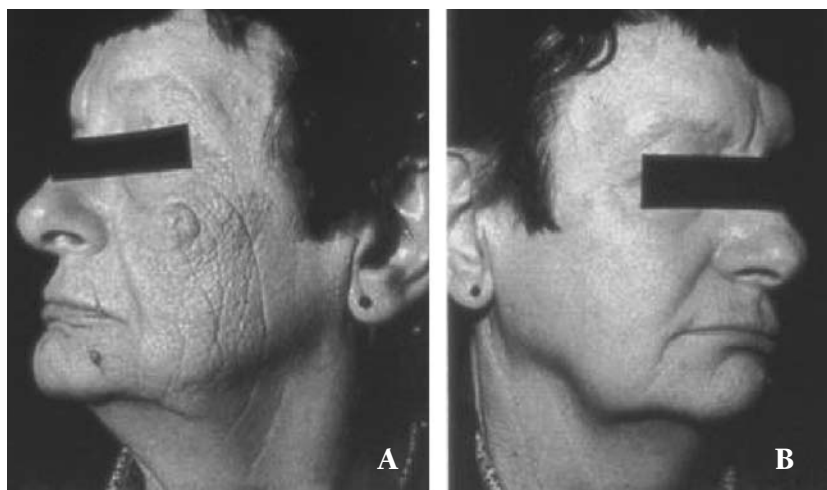


Figure 1. Unilateral elastosis with cysts and comedones caused by UVA radiation, which is not filtered by window glass. The subject had worked for 15 years in the same room, and the elastosis occurred on the side of the face that had been continuously exposed at the same orientation to a window (A). The other side of her face was not exposed to unfiltered UVA radiation (B). Reprinted with permission from Moulin G et al.¹²

fragmentation, and dispersion of collagen bundles and elastic fibers are hallmarks of photoaged skin and are due to increased activity of collagenase and elastase and decreased collagen synthesis. These changes are mediated by inflammatory processes and genotoxic effects to mitochondrial DNA, both of which can be induced by UVA and UVB radiation. Because of its deeper penetration into the dermis, UVA radiation most likely plays a more prominent role in photoaging the dermis than UVB radiation. However, UVR-induced changes to the epidermis also contribute to dermal changes through epidermis-to-dermis signaling, facilitating a possible contribution of UVB radiation to photoaging as well. Support for the prominent role of UVA radiation in photoaging is evidenced in a case following 15 years of unilateral sun exposure through window glass (Figure 1).¹²

The demand for effective photoprotection strategies that include protection against UVA radiation with the inclusion of effective UVA filters is prompted by the deleterious effects these rays have on the skin. In animal models, the UVA filter ecamsule has been shown to prevent UVA-induced histochemical alterations in skin associated with photoaging¹³ and UVR-induced changes, including pigmentation, epidermal hyperplasia, and decreased skin hydration

and elasticity, in humans.¹⁴

IN VIVO MEASUREMENT OF UVA PROTECTION

Several in vivo methods have been proposed to measure UVA-protection effectiveness, including immediate pigment darkening, persistent pigment darkening (PPD), and protection factor for UVA (PFA).¹⁵ Each has advantages and limitations when used to measure the actual UVA-protection levels in sunscreens (Table). Among these methods, PPD is a widely used UVA-protection measurement because pigmentation remains stable between 2 and 24 hours after exposure and because it is sensitive for all UVA filters regardless of their absorbency range within the UVA spectrum.¹⁵

CRITICAL WAVELENGTH: IN VITRO UVA PROTECTION MEASUREMENT

In vitro tests have been described as well, most of which are based on some manipulation of spectrophotometric measurements. One of these tests, the critical wavelength (CW), uses in vitro UV substrate spectrophotometry and subsequent calculation of the CW value to measure the absorption spectrum of a sunscreen.¹⁶ The absorption spectrum is reduced to a single index, or CW, which is defined

In Vivo Methods of Evaluating UVA Protection*

Method	Advantages	Disadvantages
IPD—measures the threshold UVA dose that is necessary to produce IPD, which is a blue-gray color from melanin oxidation in the skin after UVA exposure	Can be done in a single visit Has a short exposure time	Has a transient end point that requires immediate reading within 2 hours Works only on Fitzpatrick skin types IV and V
PPD—measures the UVA dose that is necessary to produce minimal PPD	Provides a stable end point at 2–24 hours Works in a broader range of Fitzpatrick skin types, from II to V Is sensitive to all UVR filters irrespective of absorbency range within the UVA spectrum	Requires a higher dose Requires a more powerful light source Requires a longer exposure time
PFA—measures the ratio of the amount of time it takes to produce minimal erythema or tanning on protected versus unprotected skin	Provides a stable end point at 2–24 hours Is effective on all Fitzpatrick skin types	Requires a higher dose Requires a more powerful light source Requires a longer exposure time Gives an uneven representation of UVA, with a larger role for UVA-2 (320–340 nm) 9.7757 in*IPD indicates

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as the wavelength at which the integral of the spectral absorbance curve reaches 90% of the integral from 290 to 400 nm. The CW value is based on the inherent shape of the absorbance curve rather than its amplitude; therefore, it is independent of undesirable variables that are characteristic of other in vitro calculations of absolute protection factors, such as application thickness.¹⁶

An important benefit of CW is that it does not require exposure to high-dose, nonterrestrial UVR. It is a simple, reproducible method that is largely independent of SPF, yet it ensures a measure of long-wavelength UVA protection that is commensurate with SPF.¹⁶ However, this method has its disadvantages; it does not allow the measurement of water resistance and the skin-sunscreen interaction cannot be evaluated in vitro.

CONSENSUS CONFERENCE ON UVA PROTECTION OF SUNSCREENS

The AAD Consensus Conference on UVA Protection of Sunscreens was organized in 2000 to generate agreement among AAD members, industry, and the photobiology community to provide recommendations to the FDA on the methods of testing, assessing, and labeling sunscreen products.¹ Members of the panel agreed that SPF values reflecting UVB protection should be the primary consideration for sunscreen potency. Furthermore, for a sunscreen to be labeled *broad-spectrum*, a CW value of at least 370 nm must be combined with either PPD or PFA, and a 4-fold or greater increase in the PPD or PFA value with the sunscreen must be obtained. In addition, increases in SPF must have proportional increases in UVA protection. It is insufficient to label a product as “broad spectrum”; rather, labeling for UVA protection should be pass-fail based on the foregoing criteria.¹

Unlike UVB protection, UVA protection is measured using diverse methods, but there remains an absence of a meaningful, clinically relevant biologic marker. As there is no formal UVA-labeling method for sunscreens, current UVA labeling can be confusing. Until there is a more definitive, widely accepted method for accurately measuring UVA protection in sunscreens, it is necessary to recommend sunscreens with SPF 15 or higher that include highly UVA-protective agents as part of a photoprotection regimen.

BROAD-SPECTRUM FILTER TECHNOLOGY

Broad-spectrum photoprotection can be achieved by the body's endogenous defenses, including light scattering via corneocytes, UVR-induced oxidation of urocanic acid, and oxidation of melanin. Sunscreen-

filter technology enhances the body's endogenous protection by mimicking these mechanisms. Inorganic sunscreen actives, such as zinc oxide and titanium dioxide, function primarily by light scattering, whereas organic sunscreen actives, including UVB sunscreens and avobenzone, function by absorbing UV energy and transforming radiation to heat through resonance delocalization.¹⁷

UV FILTER STABILITY

The photostable efficiency of an organic filter is key to the efficacy of a sunscreen. When UVR is absorbed through a photounstable filter, the radiation reaches an excited state followed by degradation of the molecule, meaning that it can no longer provide photoprotection. A photostable filter, however, can provide a continuum of photoprotection because after the molecule is excited to a higher state, that energy is released and returned to its ground state; it is then able to continue the cycle of protection by absorbing another photon.¹⁷ Inorganic filters also provide important UVR-protective features. These physical filters not only reflect or scatter the majority of UVR but also have a longer active life span on the skin surface.

COMMONLY USED ORGANIC UVA FILTERS

Meradimate is a very effective, highly stable UVA filter with a low incidence of allergenicity, but its peak absorption is 336 nm. In addition, its thick, sticky attributes require the use of secondary and tertiary filters to achieve an aesthetically pleasing formulation with broad-spectrum photoprotection. Oxybenzone is an oil-soluble UVB filter that has demonstrated some allergenicity but provides only weak UVA photoprotection (320 nm), so it too must be combined with other filters. Avobenzone is an excellent blocker of long-wavelength UVA rays but is unstable and denatures by 36% after UV exposure. Mexoryl SX is a recently FDA-approved sun filter that targets short-wavelength (320–340 nm) UVA rays.

COMMONLY USED UVB AND INORGANIC FILTERS

Octisalate, homosalate, and trolamine salicylate demonstrate minimal allergenicity. Because they are weak UVB absorbers with maximal absorption at 300 to 310 nm, they are generally used in combination with other UVR filters. Octinoxate, a cinnamate filter with maximal absorption at 305 nm, provides excellent stability with only 4.5% degradation after UVR exposure. However, it cannot be combined with avobenzone. Titanium dioxide and zinc oxide are both inorganic white particulates. Titanium dioxide is typically used in its micronized form, which

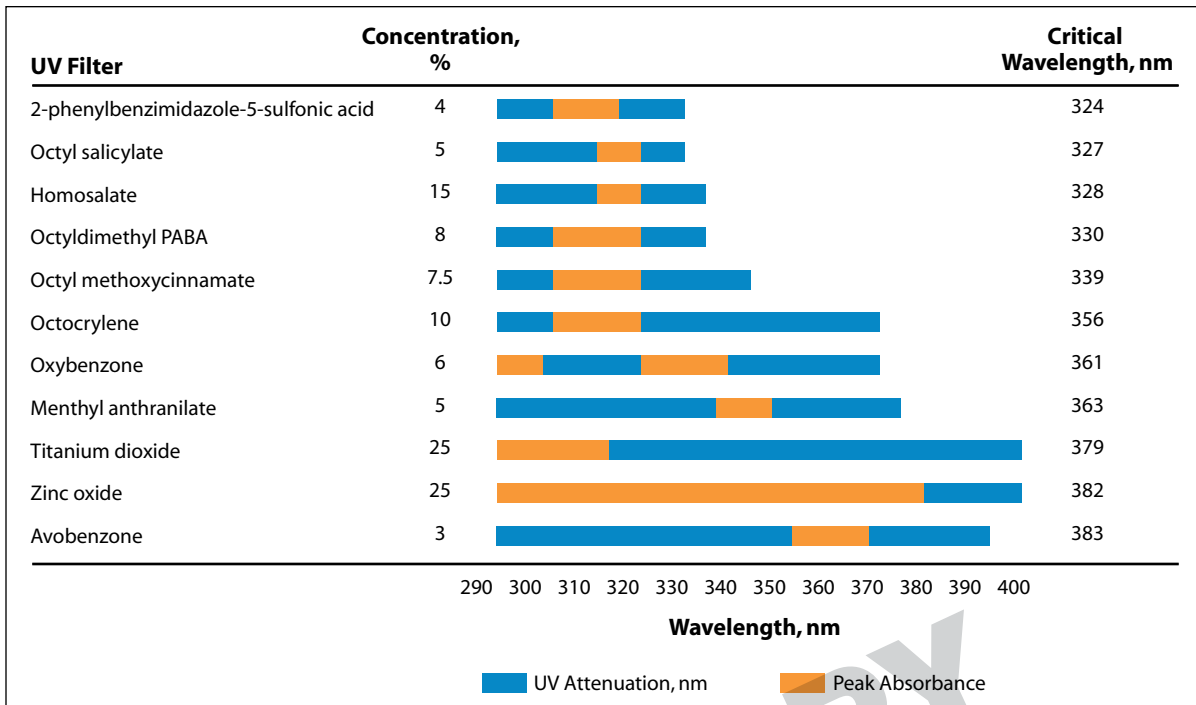


Figure 2. Absorption spectra of UV filters. PABA indicates para-aminobenzoic acid.

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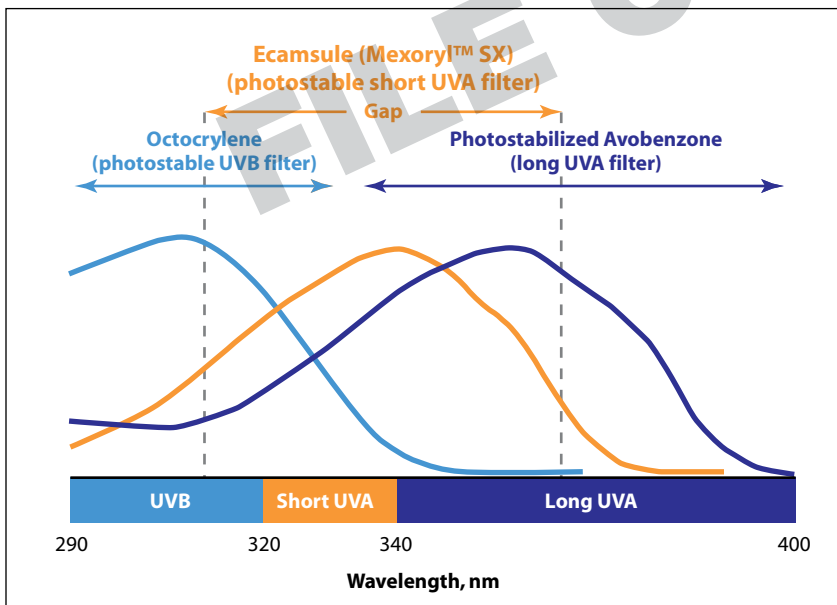


Figure 3. Complete broad-spectrum UVA and UVB protection provided by octocrylene, ecamsule, and avobenzone.¹⁸

pick a combination of organic and inorganic filters for broad-spectrum protection. The absorption chart of UVR filters (Figure 2) shows how filters are chosen for combination by their absorption spectra.¹⁶ Ideally, complementary filters are selected by their peak absorbance to cover the widest range of the spectrum possible. The combination of octocrylene, ecamsule, and avobenzone filters is ideal, providing protection over a broad wavelength of the UV spectrum (Figure 3).¹⁸ When constructing the ideal broad-spectrum sunscreen, it is of utmost importance to choose compatible filters that cover the entire UVA/UVB spectrum and ensure photostability and

allows for larger particles and better photoprotection; however, larger particles mean greater white residue on the skin. Zinc oxide can be formulated as uniform microfine particles, which improves the aesthetics of the product but provides less photoprotection.

When creating a sunscreen product, it is necessary to

functional longevity on the skin.

CONCLUSIONS

The contribution of UVA radiation to skin cancer and photoaging is significant. The authors hope that additional studies will develop more direct

measurements of how well sunscreens protect against UVA radiation with the eventual use of skin cancer prevention and photoaging as end points versus the current use of such surrogates as pigmentation and erythema. However, progress toward complete UVA protection has been made with the introduction of new UVA filters, which, in combination with other carefully selected actives, provide better broad-spectrum UVR protection.

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