Because encouraging sunscreen use is a common goal of dermatologists, it is important to be aware of factors that hinder compliance. Indeed, it is estimated that the average American adult uses less than a bottle of sunscreen annually. Included in this review is a discussion of the common side effects and controversies regarding current FDA-approved sunscreens, with a brief description of the different categorizations of sunscreen filters. Recent development of an oral pill is also discussed.

SUNSCREEN FILTER CATEGORIZATION

The UV filters of topical sunscreens are categorized based on their chemical properties and mechanism of action as either organic or inorganic. Organic sunscreens are aromatic compounds that are further subdivided by protection against UVA, UVB, or both. Although easier to apply than inorganic agents, (such as zinc oxide and titanium dioxide), they degrade more rapidly and are not as well tolerated. Conversely, while inorganic filters last longer and are better tolerated, their opacity results in a “whitening effect” that is aesthetically displeasing to some consumers. Thus, most sunscreens employ a mixture of the two filter types.

THE IMPORTANCE OF BROAD-SPECTRUM SUNSCREENS IN PROTECTING AGAINST BOTH UVA AND UVB

Solar UV radiation not absorbed by the stratospheric ozone layer is comprised of 95 percent UVA (315-400 nm) and five percent UVB (280-315 nm). UVA and UVB differ in many aspects. UVA depends less on season, latitude, time of day, and ozone layer thickness than UVB. Moreover, UVA penetrates glass, whereas UVB is absorbed, making it possible to receive high doses of UVA while indoors. Whereas the majority of UVB is absorbed in the stratum corneum, with only 10 percent reaching the superficial dermis, UVA is absorbed minimally by the epidermis. Accordingly, UVB has a predominant role in lesions primarily affecting the epidermis, such as skin cancer, sunburn, and immunosuppression. Conversely, UVA damages collagen fibers within the dermis, ultimately resulting in wrinkled, leathery skin characteristic of photoaging.

While studies have attributed the majority of epidermal events to UVB and dermal events to UVA, it is important to note that neither of these findings is mutually exclusive. For instance, while the majority of epidermal events are attributed to UVB, 10-20 percent of sunburn and mutagenesis is still attributed to UVA.

ORGANIC UVA SUNSCREEN

Of the FDA approved UVA organic filters, i.e. benzophenones and meradimate, avobenzone is superior in providing long-range UVA protection. Nevertheless, due to its photo-instability, it must be combined with photostabilizers. Thus far, octocrylene has been the most effective photostabilizer. In addition to enhancing the stability of avobenzone and many cosmetic agents, octocrylene is a broad-spectrum filter that is often combined with other filters, particularly cinnamates, to enhance their SPF. While its use has increased drastically in the past 15 years, there has been controversy given reports of photoallergy in children and in adults with a history of allergy to ketoprofen. Ketoprofen exposure has also been associated with cross-reactivity to oxybenzone due to their similarity in structure. It is important to note that the studies in which octocrylene allergic contact der-
matitis has been reported have been specifically in patients presenting with concurrent skin conditions and/or a history of ketoprofen gel. Accordingly, these studies are not representative of the entire population.

Avobenzone has also been combined with oxybenzone, a combination that has been shown to provide comparable, if not superior, UVA coverage to inorganic filters. The controversy regarding oxybenzone’s estrogenic effects is discussed in detail below. As an alternative or supplement to avobenzone combined with stabilizers, ecamsule, approved by the FDA in 2006, is a broad-spectrum filter that offers comparable UVA protection while being more photostable than avobenzone. Less than 0.1% is absorbed systemically.

OXYBENZONE CONTROVERSY

Benzophenones, particularly oxybenzone, are broad-spectrum filters used in 60 percent of US sunscreen products and are also used in photoprotective fabrics. Nevertheless, the use of oxybenzone has been questioned due to studies that have reported a high degree of contact allergy and estrogenic effects.

Although oxybenzone is the most frequently reported allergen in sunscreens, it is important to note that overall, sunscreen allergy is relatively rare (<1 percent of cases of allergic contact dermatitis in the US). Because it is a common constituent of sunscreen, it should inherently result in more reports of allergic reactions than other less common components. Controlled studies have not found a significant correlation between oxybenzone and contact allergy. For instance, in an analysis of 19,570 participants testing 89 different sunscreens consisting of 1-6% oxybenzone, Agin, et al. report that only 48 participants demonstrated sensitivity, which did not correlate with oxybenzone concentration. Overall, the rate of contact allergy attributed to oxybenzone was 0.07 percent.

Studies have reported estrogenic effects resulting from systemic oxybenzone absorption. However, the extent to which oxybenzone is absorbed in order to produce these effects is still questionable. While Hayden, et al. found one to two percent of oxybenzone to be absorbed over a 10-hour period, the study employed six times the recommended thickness and only consisted of nine people. A study in rats that showed a 23 percent increase in uterine weight upon oxybenzone exposure also employed excessive doses (Schlumpf, et al.). Specifically, the dose needed to reach significance was >1,500mg/kg/day.

Given the estrogenic effect demonstrated in rats and systemic absorption in humans, estrogenic effects in humans is a valid concern. While it has been shown that oxybenzone is absorbed systemically, the levels necessary to provoke an estrogenic response are, as reported by Wang, et al., “essentially unattainable.” Specifically, they calculated that in order to reach the high levels of sunscreen applied by Schlumpf, et al., it would take 69.3 years to attain the same dosage of sunscreen that the rats were exposed to in four days if applied once a day to the entire body and 277 years if applied only to the face, neck, hands, and arms.

Similarly, Janjua demonstrated that when oxybenzone is applied in practical amounts (2mg/cm² once daily for one week, 10% concentration, in 32 volunteers), it is systemically absorbed but does not alter hormone levels (testosterone, estradiol, inhibin B).

ORGANIC UVB SUNSCREEN

UVB filters include PABA derivatives, cinnamates, salicylates, ensulizole, and benzophenones.

Aminobenzoates include PABA and its derivative, padimate O. PABA is particularly notable for its ability to withstand water, towel-drying, and exercise. However, it became unpopular in the 1980s because it was shown to cause phototoxicity. As a result, products labeled “PABA free” became desirable. While its derivative padimate O demonstrates similar resilience but with less photoallergy, it is used infrequently, in part because it was shown in one study in yeast to be mutagenic. These results were not confirmed by subsequent studies.

Accordingly, while padimate O is the most potent UVB absorber that is FDA-approved, cinnamates, particularly octinoxate, are more frequently used and are the next most potent. In addition to its potency, octinoxate is popular due to its water resistance, stability, and limited side effects. Other UVB ingredients include salicylates and ensulizole. Salicylates are generally used in combination with other absorbers due to their reduced potency. Ensulizole also has limited side effects and high stability and is commonly found in cosmetic moisturizers, as its water solubility makes it less greasy and more aesthetically pleasing.

PHYSICAL BLOCKERS

Physical blockers (titanium dioxide and zinc oxide) are
noteworthy for their safety and broad-spectrum protection. Despite their effectiveness, their use was limited until nanosized versions were developed, as these minimize the whitening typically observed with inorganic filters. Zinc oxide offers more UVA protection, though both titanium dioxide and zinc oxide are still categorized as broad spectrum.22

In addition to minimizing the whitening effect, nanoparticles enhance the stability of organic filters23 and increase the relative SPF. This augmentation is suggested to result from the ability of smaller particles to pack more effectively, thereby minimizing empty, unprotected space.24

Clearly, despite the benefits, the safety of nanoparticles is of concern. Determining whether nanoparticles penetrate the stratum corneum is of vital importance in evaluating whether the production of free radicals threatens safety. Indeed, the stratum corneum is the rate-limiting barrier between the internal and external environment.25 Many studies, including those done by the FDA and a consortium of seven European universities, have shown that nanoparticles only penetrate hair follicles, and from there do not penetrate deeper into the skin, even that which is damaged.26,27,28

Of note, nanoparticles in sunscreens are not the only nanoparticles to which people are exposed. Other nanoparticles include silver nanoparticles in sheets and clothing, carbon nanoparticles in bicycles, and clay nanoparticles in beer bottles. Other than its application to sunscreens, TiO2 is used in paints, cosmetics, food colorants, pharmaceuticals, glass cleaners, etc. The potential toxicity of all of these nanoparticles is an active area of research.29,30

**SUNSCREEN USE RESULTING IN INCREASED SUN EXPOSURE**

Sunscreen use has been associated with increased incidence of UVR-induced pathology not because the sunscreen in itself is ineffective, but because it provides a sense of security to consumers, leading them to spend more time in the sun. Autier, et al. (2007) found in a review of five studies that duration of sun exposure increased by 13-39 percent among sunscreen users in a group of people intentionally seeking sun exposure.31 Accordingly, without proper patient education that sunscreen does not provide complete protection from the sun, sunscreen use can become counterproductive.

**SUNSCREEN AND VITAMIN D**

Adequate vitamin D is essential for facilitating intestinal absorption of calcium to prevent resorption of bone. Thus, vitamin D deficiency can present as osteoporosis or osteomalacia in adults or rickets in children. Low vitamin D has also been associated with autoimmune disease, depression, pregnancy complications, certain cancers, and the development of type 1 diabetes.32 Not only are the number of dietary sources of vitamin D relatively scarce (certain fish, such as salmon, sardines, and tuna, shiitake mushrooms, egg yolk), the quantity of vitamin D obtained from each of these sources is much less than that obtained from the sun—90 percent of vitamin D in the body is formed via the cutaneous rather than the oral route.33

The importance of vitamin D and the carcinogenic effects of the sun presents a paradox. While too much sun in itself is the major risk factor for skin cancer, exposure to the sun significantly augments vitamin D levels, and studies have shown a correlation between vitamin D deficiency and skin cancer. For instance, mutations in the vitamin D receptor have been associated with melanoma progression.34 Nevertheless, some studies have shown no difference in vitamin D levels of melanoma patients.35

Considering the fact that UVB exposure is responsible for most vitamin D production, there has been considerable controversy regarding the use of sunscreen and its effect on vitamin D synthesis. Vitamin D deficiency is more prevalent in dark-skinned individuals because melanin effectively absorbs UVB rays. Analogously, sunscreen absorbs UVB rays, thereby limiting vitamin D synthesis.36 While the importance of sunscreen use has become increasingly emphasized,37 since 1988, vitamin D deficiency has increased.38

In one study, Young exposed 60 volunteers to sunlight for a week in order to compare the effect of sunscreen on vitamin D production. While vitamin D production was still augmented with sun exposure in the sunscreen applying group (2mg/cm2, three times per day), it was significantly less increased as compared to control (13nmol/L broad-spectrum, 19nmol/L small spectrum, 28nmol/L control).39

Despite the fact that sunscreen has been shown to decrease vitamin D synthesis, it is still possible to attain adequate sunlight needed for vitamin D synthesis without causing photodamage. Just five minutes of sun exposure without sunscreen is sufficient in fair-skinned individuals. With sunscreen of SPF 15, 20 minutes is recommended.40,41 It is advised that people at greater risk of vitamin D deficiency increase their oral intake rather than seek excess sun exposure due to the risk of skin cancer.

**NEW DEVELOPMENTS: ORAL PILL**

Extracts of the tropical fern, *Polypodium leucotomos* (PL), have been shown to be beneficial as an adjunct to sunscreen in the prevention of UVR-induced skin tumor progression and inflammatory conditions. Reduced tumor progression in PL-treated mice is likely mediated by an increase in p53 expression and decrease in pyrimidine dimers and reactive oxygen species.42,43 PL has been indicated for inflammatory conditions such as atopic dermatitis due to its inhibition of inflammatory mediators.44 Of note, Ramírez-Bosca, et
CONCLUSION

Among the most common concerns potentially limiting sunscreen usage are fear of photosensitivity and contact dermatitis. In particular, oxybenzone has generated concern regarding potential estrogenic effects. These concerns should not prevent the physician from advising adequate sunscreen use. The current literature suggests that cases of photosensitivity and contact dermatitis are generally limited to a rare set of susceptible individuals, and the levels of oxybenzone necessary for estrogenic effects are nearly unattainable. Furthermore, the apparent increase in sun exposure with concomitant sunscreen use should not detract physicians from recommending a daily sunscreen. Rather, patient education is essential.

The authors received no Funding/Support and reported no Financial Disclosure.

University College of Medicine, Boca Raton, FL. Angela G. Weatherall, MD is a practicing dermatologist at ClearlyDerm for Dermatology and in the Department of Clinical Biomedical Science, Florida Atlantic University Charles E. Schmidt College of Medicine, Boca Raton, FL.


54. de Groot AC, Roberts DW. Contact and photocontact allergy to octocrylene: a review. Contact Dermatitis. 2014;70:193–204.

55. de Groot AC, Roberts DW. Contact and photocontact allergy to octocrylene: a review. Contact Dermatitis. 2014;70:193–204.


