Current challenges in photoprotection

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Electromagnetic radiation in the ultraviolet, visible, and infrared ranges all produce biologic effects. Ultraviolet filters are the most well-studied photoprotective measure for the adverse effects of ultraviolet radiation. Because of the reported endocrinologic effects of oxybenzone in animal studies, its effects on coral reefs, and its photocontact allergy potential, its use has been minimized in many countries worldwide. New developments in topical antioxidants and oral and subcutaneous agents (eg, Polypodium leucotomos extract, afamelanotide, nicotinamide) with photoprotective and antiphotocarcinogenic properties could potentially provide addition modalities for protection against the effects of visible light and infrared radiation. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.09.040.)

Key words: afamelanotide; antioxidant; nicotinamide; oxybenzone; photoprotection; Polypodium leucotomos extract; sunscreen.

Although the need to prevent acute (erythema) and chronic (skin cancer and photoaging) skin damage resulting from exposure to ultraviolet (UV) radiation (UVR) (UVB and UVA) is well understood, the safest and most effective way to achieve this still presents a number of challenges, specifically, in the practical implementation of sunprotective measures. These include concerns about the safety of some currently available UV filters, whether sunscreens detrimentally affect serum vitamin-D levels, whether new nontopical agents can offer significant additional sun protection, and how to protect against recently identified harmful effects of radiation at frequencies outside the UV range of the solar spectrum.

It should be emphasized that although sunscreen products are excellent means of photoprotection, they should always be part of the total photoprotection package, which includes seeking shade, wearing protective clothing and a wide-brimmed hat, and using sunglasses.

Abbreviations used:

25(OH)D:	25-hydroxyvitamin D
CPD:	cyclobutane pyrimidine dimer
EPP:	erythropoietic protoporphyria
FDA:	Food and Drug Administration
MMP:	matrix metalloproteinase
ROS:	reactive oxygen species
SPF:	sun-protection factor
UV:	ultraviolet
UVR:	ultraviolet radiation

SUNSCREEN SAFETY AND EFFICACY

Oxybenzone

Oxybenzone (benzophenone-3) is an organic filter that absorbs both UVB and short-range UVA (UVA2). Because few other organic UVA filters have been approved by the US Food and Drug Administration (FDA), oxybenzone is widely used in the United States. Concerns were expressed about the safety of oxybenzone after reports of cases of allergic and photoallergic contact dermatitis and

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because of its potential for endocrine disruption reported in an animal model. Oxybenzone is the most common photoallergen among all the UV filters.[1] A 10-year retrospective analysis found that 70.2% of almost 24,000 patients patch-tested with UV filters between 2001 and 2010 had positive reactions to oxybenzone.[2] In 2014, oxybenzone was largely responsible for the naming of benzophenones as contact allergen of the year by the American Contact Dermatitis Society.[3] Potential endocrine effects of oxybenzone were identified in several in vitro studies[4-6] and an in vivo study showed dose-dependent estrogenic activity in 21-day-old rats fed doses of oxybenzone (≥1500 mg/kg/d).[7] It should be noted that the doses of oxybenzone used in the animal study were very high and the estrogenic potency detected was 1 million-fold less than the estradiol control.[8,9] Short-term studies that looked at topical application of UV filters including oxybenzone in human beings found that there were no significant UV filter—related alterations on the endocrinologic effects on either reproductive hormones[10] or thyroid function.[11] Mathematic modeling indicated that it would take 277 years using a sunscreen containing 6% oxybenzone used at 2 mg/cm^2 (the dose recommended for sun-protection factor [SPF] testing by the FDA) or 1 mg/cm^2 (reported real-life use) to achieve the systemic levels of oxybenzone achieved in the study in rats.[12] Oxybenzone has been in use in the United States since at least the early 1970s with no clinical report of estrogenic side effects. Thus, all current data indicate that oxybenzone is safe. Nonetheless, in the European Union the label of a sunscreen containing oxybenzone must include a cautionary statement ("contains benzophenone-3") if the concentration is over 0.5%.[13] Oxybenzone has also emerged as a potential hazardous environmental contaminant. Water sampling studies have shown that it is not fully eliminated during waste water treatment,[14,15] and oxybenzone and its metabolites have been detected in fish, with antiandrogenic and antiestrogenic effects.[16,17] A genotoxic effect of oxybenzone on coral was recently reported in a laboratory study,[18] supporting earlier evidence of bleaching effects on coral in the Atlantic, Pacific, and Indian oceans,[19] and presenting a hazard to the viability of the reefs.

Outside the United States oxybenzone has been replaced in many sunscreens by other UV filters. These include broad-spectrum filters such as bemotrizinol and bisoctrizole, which are not currently available in the United States, and ecamsule, which is available in the United States only in products approved though the New Drug Application process. In 2015 the FDA announced that ecamsule, bemotrizinol, bisoctrizole, and 5 other sunscreen ingredients that had been awaiting approval in the United States through the Time and Extent Application process were not generally recognized as safe and effective, despite approval by regulatory agencies in many parts of the world.[20]

CAPSULE SUMMARY

- In addition to application of sunscreen, proper photoprotection consists of seeking shade, wearing photoprotective clothing and hat, and using sunglasses.
- Ultraviolet filters have been well established to be effective against the adverse effects of ultraviolet radiation.
- With increased understanding of the effect of visible light and infrared radiation, studies on antioxidants and oral and subcutaneous topical forms of photoprotection are ongoing.

Antioxidants

Traditional sunscreens provide effective protection against erythema but not similarly effective protection against the generation of reactive oxygen species (ROS) in the skin after exposure to UVR, especially UVA.[21] Therefore, antioxidants are incorporated in many sunscreen products because of their ability to scavenge and reduce levels of ROS, the primary mediator of oxidative damage to the skin.[22-24] Compared with sunscreen alone, the addition of antioxidants has been shown to suppress ROS formation by an additional 1.7-fold for SPF 4, and 2.4-fold for SPF 15 and 50 formulas, respectively.[25] Sunscreen with added antioxidant has been shown to be more efficient than sunscreen alone in suppressing other changes in the skin known to be induced to exposure to UVR such as development of pigmentation, depletion of Langerhans cells, and induction of matrix metalloproteinase (MMP)-9.[22-24] These and other data indicate that addition of antioxidants to sunscreens represents a potentially effective strategy to minimize UV damage. The antioxidants that have been studied include vitamins A (retinol), C (ascorbic acid), and E (α-tocopherol), and (−)-epigallocatechin-3-gallate, a polyphenol component of green tea. Antioxidants are inherently unstable compounds, however, so are difficult to formulate in an acceptable, stable, and biologically active composition for sunscreen products. A 2011 analysis of 12 commercially available US sunscreens