Title:

Sunscreens – what’s important to know
Christina Antoniou*, Maria G. Kosmadaki*, Alexandros J. Stratigos, Andreas D. Katsambas
Department of Dermatology
University of Athens, School of Medicine
Andreas Sygros Hospital
Athens, Greece

Corresponding author: Prof. Andreas Katsambas
Department of Dermatology
University of Athens
Andreas Sygros Hospital
5 Ionos Dragoumi Street
Athens 16121
Greece
Email: katsabas@internet.gr

* These authors contributed equally to the work.
Abstract

The popularity of sunscreens dramatically increased since ultraviolet irradiation was implicated in the pathogenesis of skin cancer and skin aging. The absorption properties, safety, photostability of different organic and inorganic filters are reviewed: PABA, salicylates, cinnamates, benzophenones, butylmethoxydibenzoylmethane (Parsol 1789), drometrizole trisulphonic (Mexoryl XL), terephthalhydene dicamphor sulphonic acid (Mexoryl SX), methylene bisbenzotriazol tetramethylbutylphenol (Tinasorb M), anisotriazine (Tinasorb S), titanium dioxide and zinc oxide. Furthermore, this review discusses the optimal methods for measuring the protection that a sunscreen offers, the role of sunscreen use in melanoma prevention and future trends in sunscreen filters development.
Introduction

Extraterrestrial sunlight includes x-ray, ionizing, ultraviolet, visible, and infrared radiation, and radiowaves. The solar spectrum at the earth’s surface (sea level) consists of wavelengths of electromagnetic energy only between 290 and 3000 nm, while the spectrum implicated in human skin reactions involves wavelengths up to 1800 nm. **Ultraviolet (UV) radiation is arbitrarily subdivided into three bands**, UVA (320-400 nm), UVB (290-320 nm) and UVC (200-290 nm). The total flux of UVA at the earth’s surface vastly exceeds that of UVB, with all the UVC being completed absorbed by stratospheric ozone. Depending on the latitude, the time of the day and the season of the year, the terrestrial spectrum of solar UV radiation consists of 1–5% of UVB radiation and 95–99% of UVA radiation. UVB radiation is fully absorbed by the stratum corneum and the top layers of the epidermis, whereas up to 50% of incident UVA radiation penetrates Caucasian skin deep into the dermis. There is now a heightened concern regarding the depletion of the stratospheric ozone layer by the chlorofluorocarbons, halons, and nitric oxides. This may result in a increased irradiance level of both UVB and UVC at the earth’s level that may eventually contribute to a higher incidence of skin cancer and other harmful effects to humans and to other life forms.

Ultraviolet irradiation is involved in the pathogenesis of skin cancers, causes premature aging of the skin and photoimmunosuppression. It also plays a role in the pathogenesis of photosensitive diseases such as chronic actinic dermatitis, polymorphous light eruption, actinic prurigo, hydroa vacciniforme, and photoallergic or phototoxic drug reactions. Both UVB and UVA radiation may effect the biomolecules of the skin. Specifically, UVB is directly absorbed by DNA, giving rise to dimeric photoproducts between adjacent pyrimidine bases. Two types of lesions are produced: cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6-4) pyrimidone photoproducts. Both may lead to mutations (if they are not repaired) that appear to have a role in photocarcinogenesis. A high proportion of p53 mutations is detected at bipyrimidine sites in skin tumors. Furthermore, UVB photoisomerizes trans- to cis-urocanic acid (a prominent candidate chromophore for mediating photoimmunosuppression) and generates reactive oxygen species (ROS), suggesting that UVB also employs an indirect mechanism for its detrimental effects.
The contribution of UVA on the effects of UV on the skin is also currently recognized. It induces the formation of ROS that react with membrane lipids and amino acids. Membrane damage results in the release of arachidonic acid and leads to activation of secondary cytosolic and nuclear messengers that activate UV-response genes. **UVA is further shown to induce photocarcinogenesis in mice**. Basal keratinocytes from human skin squamous cell carcinomas contained UVA signature mutations. Exposure of normal human cultured fibroblasts to UVA induces the same type of DNA mutations (pyrimidine dimmers) as UVB. UVA also results in immunosuppression affecting both the induction (primary sensitization) and elicitation of immune responses and has an important role in photoaging.

The avoidance of unwanted skin effects of the sun, termed photoprotection, has become very popular in recent decades and involved into a public policy concern. The protective measures that can be taken are avoidance of the sun, protection through clothing, the use of sunscreen filters. **The latter are shown to have a protective role against photocarcinogenesis, photoimmunosuppression and photoaging** and have become an essential armament for dermatologists in providing protection to human skin against adverse effects of solar radiation.

**Sunscreens**

Sunscreens have traditionally been divided into organic (chemical) absorbers and inorganic (physical) blockers on the basis of their mechanism of action. The organic compounds absorb high-intensity UV rays with excitation to a higher energy state. Excess energy is dissipated by emission of higher wavelengths or relaxation by photochemical process such as isomerization and heat release. They include PABA and PABA esters, salicylates, cinnamates, benzophenones, butylmethoxydibenzoylmethane (Parsol 1789), drometrizole trisulphonic (Mexoryl XL), terephthaldehyde dicamphor sulphonic acid (Mexoryl SX), methylene bisbenzotriazol tetramethylbutylphenol (Tinasorb M), anisotriazine (Tinasorb S). The inorganic agents, that protect the skin by reflecting and scattering UV, are titanium dioxide and zinc oxide.
Para-aminobenzoic acid (PABA) ($\lambda$ maximum, 283 nm) is one of the first widely available organic sunscreen ingredients. It is a very effective UVB filter when used in a 5% concentration in 50% to 60% alcohol base\textsuperscript{16}. It penetrates deep into the dermis with high resistance from water and perspiration. Because PABA was shown to be carcinogenic in vitro\textsuperscript{17} and to cause allergic reactions (contact and photoallergic) its current use in sunscreen formulations is limited. The most commonly used PABA derivate is octyl dimethyl PABA or padimate O ($\lambda$ maximum, 311 nm). It is effective UVB filter with a good safety profile, although less effective than PABA.

Salicylates absorb UV irradiation from 300 – 310 nm and are thus weak UVB filters. However, they are very stable and water-insoluble. Skin sensitization and photocontact sensitization reactions to topical application of salicylates are rare. Octisalate (octyl salicylate; $\lambda$ maximum, 307 nm) and homosalate (homomenthyl salicylate; $\lambda$ maximum, 306 nm) are commonly used for improved substantivity and reduced photodegradation of other sunscreen ingredients, including oxybenzone and avobenzone\textsuperscript{18}. Less than 1% of the applied dose of octyl salicylate penetrates through human skin\textsuperscript{19} and this is similar to dermal penetration of homosalate.

Octinoxate (octyl methoxycinnamate or OMC or Parsol MCX) is the most common cinnamate and probably the most common UV filter used globally ($\lambda$ max 311 nm). It is frequently used in combination with other UVB absorbers to achieve high SPF values in the final product. Topical application of OMC is tolerated well: skin irritation is almost negligible and photocontact dermatitis is rare\textsuperscript{20-22}. Upon exposure to sunlight octinoxate degrades into a photoproduct with less UV absorbing ability. Several studies suggest ways to improve the photostability of cinnamate. Encapsulation of ethylhexyl-p-methoxycinnamate into nanoparticles consisting of poly- D,L-lactide-co-glycolide results in a reduction of the photodegradation of this from 52.3% to 35.3%\textsuperscript{23} and glyceridic esters of octinoxate have a longer photoprotective property in vivo compared with the native molecule\textsuperscript{24}. Systemic absorption of octinoxate has been measured but it is considered of no toxic concern\textsuperscript{25}.

Benzophenones absorb UVB and some UVA (to approximately 360 nm, with a peak at 290 nm). The most popular benzophenone and one of the most common sunscreen ingredients is benzophenone-3 or oxybenzophenone. It has been isolated in the blood and urine of humans\textsuperscript{25-27} after topical application. Compared with other UV-filters benzophenone-3 is the most bioavailable following topical application –
however this bioavailability is not of toxicologic concern \textsuperscript{25,28}. Moreover, it has the highest reported incidence of photodermatitis \textsuperscript{29}.

\textbf{Parsol} 1789 or avobenzone or butyl methoxydibenzoylmethane is a very efficient UVA filter since it absorbs across the UVR (290 – 400nm). Importantly, however, is not photostable. Inclusion of other filters that act as stabilizers can reduce its photodegradation. The systemic bioavailability of avobenzone is limited - its dermal penetration is less than or equal to 1\% of the applied dose \textsuperscript{30,31}. It can cause photoallergy but apparently less frequently than other UV filters. Diethylamino hydroxybenzoyl hexyl benzoate is a successor of avobenzone that has similar UV-spectral properties but superior photostability.

Terephthalydene-dicamphor sulfonic acid (Mexoryl SX; \( \lambda \) maximum, 345 nm) is a photostable, broad spectrum sunscreen, effective at absorbing irradiation between 290 and 400 nm. However, most of its UV absorptive capabilities are within the UVA range. The systemically absorbed dose of Mexoryl SX is less than 0.1\% of the applied dose \textsuperscript{32}.

Drometrixazole trisiloxane (silatriazole; Mexoryl XL) is a hydroxybenzotriazole. It is the first photostable broad UV filter against UVA and UVB. It consists of two chemical groups; 12-hydroxyphenylbenzotriazole, which absorbs both in the UVA and UVB range, and siloxane chain, which is liposoluble. It has two absorption spectra (290 – 320 nm, \( \lambda \) maximum, 303 and 320 -360 nm, \( \lambda \) maximum 344 nm). Allergic reactions to Mexoryl SX and Mexoryl XL appear to be very rare \textsuperscript{33}.

Methylene-bis-benzotriazolyl tetramethylbutylphenol (Tinasorb M) absorbs across the UVA spectrum but also has a strong absorption in UVB (\( \lambda \) max 360 nm and 303 nm). It is the first of a new class of UV filters that combine the properties of both UV conventional filters (organic and inorganic) – it scatters, reflects and absorbs UV light. It is manufactured as colorless organic microfine particles which can be dispersed in the aqueous phase of sunscreen emulsions. It is proven very photostable. Because it is relatively large, its systemic absorption is small. So far, there has been one report of contact dermatitis due to Tinasorb M \textsuperscript{34}.

Bis-ethylhexyloxyphenol methoxyphenol triazine (anisotriazine; Tinosorb S) is an oil soluble broadband absorber that protects against UVB (\( \lambda \) maximum 310 nm) and UVA (\( \lambda \) maximum 343 nm). It is photostable and can increase the photostability of avobenzone and ethylhexyl methoxycinnamate \textsuperscript{35}.
The metal oxides, titanium dioxide and zinc oxide, are the physical sunscreens. They are very efficient, photostable sunscreens that offer protection extending into the UVA and visible ranges with almost negligible irritation and sensitization potential. However, these big molecules that reflect/scatter UV can cause whitening of the skin. Therefore, the metal oxides are now frequently processed as microfine or nanoparticles (10 – 50 nm compared to 200 – 500 nm of the nonmicronized form). Nanoparticles, reflect/scatter and absorb UV, and they are transparent on the skin, thus enhancing the cosmetic acceptability of the product. However, this happens at the expense of optimal protection in the UVA and visible ranges. Microfine TiO₂ has an absorption profile greater in the UVB but extends in the long UVA. Microfine ZnO has a flat absorption profile that spans UVB and UVA. Concern has been raised regarding possible systemic absorption of the nanoparticles 36,37. TiO₂ doesn’t seem to penetrate the epidermis 38 and ZnO has limited systemic absorption, if any 39.

New sunscreen technology

Sunscreen efficiency may further augment with the use of modern sunscreen technology. Exploiting microencapsulation active sunscreen ingredients can be entrapped within a silica shell 40,41. Using this technique allergic or irritant reactions may be diminished since the active ingredient is not in direct contact with the skin. Microencapsulation may further solve incompatibility problems between different ingredients. Moreover, polymer materials that do not absorb UV irradiation but enhance the effectiveness of the active ingredients may be used. Specifically, sunspheres are tiny styrene/acrylates copolymers that are filled with water. When the product is applied to the skin, the water comes out of the sphere, leaving microscopic hallow beads. These beads scatter UV irradiation and increase the probability of contact with the active ingredients. They can boost SPF by 50% - 70% making it possible to reduce the sunscreens active ingredients.

SPF – protection against UVA - IPF

Sunscreens are very effective at preventing erythema, the endpoint used in sun protection factor (SPF) determinations. SPF is defined as the ratio of the dose of UVR (290-400 nm) required to produce 1 minimal erythema dose (MED) on sunscreen-
protected skin (after application of 2 mg/cm² of product) over the dose to produce 1 MED on unprotected skin. Importantly, absence of erythema does not equal prevention of UV-induced damage. SPF is primarily a measure of UVB protection, as UVB is 1000 times more erythemogenic than UVA. Moreover, high SPF products allow individuals to spend greater amounts of time in the sun without developing erythema (burning). These products don’t necessarily offer adequate UVA protection. Protection against UVA is becoming a major concern since UVA damage is now implicated in photocarcinogenesis, photoaging and immunosuppression.

Currently, there is no consensus about the best method for measuring UVA protection. A variety of methods have been proposed. In vivo methods have been developed among which persistent pigment darkening (PPD) is more broadly used. PPD is measured two hours after irradiation of the skin with 30 J/cm² of UVA.

An in vitro method proposed by Diffey et al., is based on the shape of the absorption spectrum of a sunscreen product, which is obtained using spectrophotometry. Critical wavelength is the wavelength where the integral of the spectral absorbance curve reaches 90% of the integral from 290 nm to 400 nm. It measures a sunscreen’s extinction capacity in the UVA range in relation to its overall extinction between 290 nm and 400 nm. The critical wavelength determination does not promote the false notion of UVB and UVA as separate entities but rather as part of continuous electromagnetic spectrum. As the critical wavelength increases, so must the protection against UVA. A complete description of a product’s photoprotective characteristics results when critical wavelength is used in conjunction with SPF. However, although this in vitro spectrophotometry measurement is useful, it lacks the relevance to a clinical/biological endpoint easily grasped by the public.

Furthermore, Immune Protection Factor (IPF) determination was introduced to measure the capacity of sunscreens to protect against immunosuppression. There are no standardized protocols to measure IPF. Current methods use solar simulated radiation (that contains UVA and UVB) and evaluate the ability of a sunscreen to inhibit UVR-induced local suppression of the contact or delayed type hypersensitivity response. The induction or the elicitation arms of these responses are being evaluated in vivo. The induction arm of the contact hypersensitivity response is sensitive to a single sub-erythema UVR exposure but it requires sensitization, a large number of volunteers and is very time consuming. The elicitation arm of the contact or delayed hypersensitivity responses uses prior sensitization to antigens but repeated UVR
exposures may be required making the use of this method difficult. A simpler method for measuring sunscreens’ immunoprotective capacity is needed. IPF probably has a better correlation with the UVA protectiveness of sunscreen than with the SPF\(^{46,47}\).  

**Photostability and Water Resistance**

In addition to how efficiently sunscreens absorb UV irradiation, their photostability is also of major concern. The sunscreen ingredients should absorb or reflect and scatter radiation throughout the period of time they are intended to provide protection for, and thus should remain stable photochemically. However, many chemical filters exhibit some photoreactivity (which may be minimal or significant) and lead to formation of a photoproduct(s) that might still act as a filter (e.g. photoisomerization reaction). Photostability depends on the filter itself, on the presence of other filters in the product and on solvent or vehicle. Many UV filters, especially avobenzone\(^{35}\), octinoxate (OMC), and octyl dimethyl PABA, are photolabile\(^{48}\). Other UV filters are frequently used in the sunscreen as they are known to increase the photostability of the final product; these include ZnO, TiO2, the salicylates, and methylbenzylidene camphor. Furthermore, the newly developed filters are photostable – they include terephthalylidene dicamphor sulfonic acid (Mexoryl SX), drometrazole trisiloxane (Mexoryl XL), methylenebis-benzotriazoyl tetramethylbutylyphenol (Tinosorb M), and bis-ethylhexyloxyphenol methoxyphenol triazine (Tinosorb S).

Resistance to water immersion and sweating is also an important aspect of a sunscreen performance. In the USA this is measured in vivo, by the ability of a product to withstand water immersion. SPF has to remain unchanged after two twenty-minutes immersions for a “water resistant” product. A “very water resistant” product will offer the same protection after four twenty-minutes immersions. Each 20 minute immersion interval is followed by a 20 minute rest/air dry period until the total water exposure time is reached. In Europe, the SPF after a 40 and 80 minute water immersion period is measured and compared to the original SPF before water exposure. A product is considered “water resistant” or “extra water resistant” if the SPF data after 40 or 80 minute immersions respectively is greater or equal to 50% of the pre-immersion SPF. Thus, the SPF number on the product label for European
sunscreen products is pre-water exposure while in the USA the SPF on the label corresponds to the measurements after the water immersion cycles.

**Sunscreens and Melanoma**

There are different reports in the literature regarding the relation of sunscreens and melanoma. Some studies have found a decreased melanoma risk with sunscreen use 18,49-51, and others increased melanoma risk among sunscreen users 52-54. Subsequently, the data have been meta-analysed to show little or no positive association of sunscreen use and melanoma 55,56.

The methodology used in the studies may explain the discrepancy. Frequency and quantity of sunscreen application and SPF of the specific products used are difficult to evaluate based on retrospective recall of participants 57-59. Furthermore, the sunscreens used probably protected only against UVB, while currently available sunscreens often have both UVA and UVB protection. In fact, individuals relying on sunscreens as their sole form of photoprotection in the past decades, may have been subject to greater cumulative sun exposure, especially in the UVA range. Furthermore, although most studies include skin phototype and sun sensitivity, the results were not statistically adjusted on sun sensitivity of study participants – i.e., individuals with increased risk for sunburn and more likely to develop melanoma but they are also most likely to use sunscreens.

Taking under consideration the above weaknesses of the conducted studies and the results from the meta-analysis showing no correlation between sunscreen use and melanoma, it is probably safe to suggest that predominantly UVB absorbing sunscreens do not prevent melanoma development in humans. The use of modern sunscreens offering broad UV protection remains to be evaluated. Despite the controversy, sunscreen use remains an important part of melanoma prevention because it can effectively block mutations 60,61 and prevent sunburn 62, factors shown to be associated with melanoma. Moreover, recent small studies with short follow-up period suggest that sunscreens probably reduce the development of melanocytic nevi, a known risk factor for melanoma 63-66.

**Future trends**

Novel substances with photoprotective potential are being investigated. T4 endonuclease V (T4N5) is a DNA repair enzyme in bacteria. It has also been shown to
accelerate the repair of DNA in human cells when it is delivered intracellularly. The topical use of T4N5 has been investigated in patients with XP, a defect in nucleotide excision repair of DNA, and found to have a protective effect on the appearance of BCC and actinic keratosis \textsuperscript{67}. Application of T4N5 immediately after UV exposure partially protects against sunburn cell formation. However, it has little or no effect on UV-induced skin edema \textsuperscript{68}.

Thymidine dinucleotide (pTT) is a small DNA fragment that induces a photoprotective response in mammalian cells and intact skin. Specifically, topical pTT pretreatment enhances the rate of DNA photoproduct removal, decreases UV-induced mutations, and reduces photocarcinogenesis in UV-irradiated hairless mice \textsuperscript{69}. The protective effects of pTT are attributed to its partial sequence homology with the mammalian telomere repeat sequence 5'-TTAGGG-3'. In mammalian cells, telomeres are tandem repeats of a short DNA sequence TTAGGG that cap chromosome ends and form a large loop structure \textsuperscript{70}. Disruption of this loop structure is hypothesized to lead to exposure of the 3'-overhang sequence (repeats of TTAGGG), digestion of the overhang, and signaling that induces DNA damage responses. It has been suggested that providing cells with DNA oligonucleotides partially or totally homologous to the telomere sequence (like pTT), initiates signalling for DNA damage-like responses without antecedent DNA damage \textsuperscript{70}. The photoprotective potential of pTT remains to be evaluated in humans.

Summary

Ultraviolet irradiation has deleterious effects that may be, at least partially, inhibited through the use of sunscreens. Development of new, highly effective sunscreens of both the traditional chemical kind as well as newer micronized physical blockers continues. It is an important task for dermatologists to educate patients regarding appropriate sun protection and to encourage prudent use of sunscreens.

References:
<table>
<thead>
<tr>
<th>Sunscreen filter</th>
<th>Wavelength protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Para-aminobenzoic acid (PABA)</td>
<td>UVB</td>
</tr>
<tr>
<td>Octisalate</td>
<td>UVB</td>
</tr>
<tr>
<td>Homosalate</td>
<td>UVB</td>
</tr>
<tr>
<td>Octinoxate</td>
<td>UVB</td>
</tr>
<tr>
<td>Oxybenzophenone</td>
<td>UVB and some UVA</td>
</tr>
<tr>
<td>Avobenzone</td>
<td>UVA</td>
</tr>
<tr>
<td>Terephthalidene-dicamphor sulfonic acid</td>
<td>UVA and UVB</td>
</tr>
<tr>
<td>Drometriazole trisiloxane</td>
<td>UVA and UVB</td>
</tr>
<tr>
<td>Methylene-bis-benzotriazolyl tetramethylbutylphenol</td>
<td>UVA and UVB</td>
</tr>
<tr>
<td>Bis-ethylhexoxyphenol methoxyphenol triazine</td>
<td>UVA and UVB</td>
</tr>
<tr>
<td>titanium dioxide</td>
<td>UVA and UVB</td>
</tr>
<tr>
<td>zinc oxide</td>
<td>UVA and UVB</td>
</tr>
</tbody>
</table>

2 Cadet J, Sage E, Douki T. Ultraviolet radiation-mediated damage to cellular DNA. *Mutat Res* 2005; 571: 3-17.
10 Dumay O, Karam A, Vian L et al. Ultraviolet AI exposure of human skin results in Langerhans cell depletion and reduction of epidermal antigen-


21 Thune P. Contact and photocontact allergy to sunscreens. *Photodermatol 1984; 1*: 5-9.


Hughes TM, Martin JA, Lewis VJ et al. Allergic contact dermatitis to drometrizole trisiloxane in a sunscreen with concomitant sensitivities to other sunscreens. *Contact Dermatitis* 2005; **52**: 226-7.

Gonzalez-Perez R, Trebol I, Garcia-Rio I et al. Allergic contact dermatitis from methylene-bis-benzotriazolyl tetramethylbutylphenol (Tinosorb M). *Contact Dermatitis* 2007; **56**: 121.

Chatelain E, Gabard B. Photostabilization of butyl methoxydibenzoylmethane (Avobenzone) and ethylhexyl methoxycinnamate by bis-ethylhexyloxyphenol methoxycphenyl triazine (Tinosorb S), a new UV broadband filter. *Photochem Photobiol* 2001; **74**: 401-6.


Young AR. Methods used to evaluate the immune protection factor of a sunscreen: advantages and disadvantages of different in vivo techniques. *Cutis* 2004; **74**: 19-23.


