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A Review of Sunscreens and Their Adverse Reactions

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SUMMARY Sunscreens are used to protect the skin from harmful effects of ultraviolet (UV) light but they do not completely prevent photocarcinogenesis, photoaging and photoimmunosuppression. They are useful for protection against UVB and short-wave UVA. Complete protection against long-wave UVA has not been achieved. There is no universally accepted method to evaluate UVA protection. Sun protection factor is a simple and internationally used method to compare sunscreen protection against UVB induced erythema. Adverse reactions to sunscreens are not common but they should be considered especially in persons with pre-existing eczematous conditions or photodermatoses. The use of sunscreens has increased steadily over the last decade; as a result, allergy and photoallergy to UV filters are now more frequent than in the past. Sensitization can occur from the various sunscreening agents and from the excipients included in formulations. An overview of sunscreens, their effectiveness, and adverse reactions is presented.

KEY WORDS: sunscreens, sun protection factor, UVA protection methods, adverse reaction to sunscreens

INTRODUCTION

The ultraviolet (UV) spectrum is divided into UVC (270 to 290 nm), UVB (290 to 320 nm), and UVA (320 to 400 nm). UVA is further subdivided into two regions: short-wave UVA or UVA II (320 to 340 nm) and long-wave UVA or UVA I (340 to 400 nm). An UVC ray does never reach the earth's surface. The atmosphere, especially the ozone layer, screens it out. UVA and UVB radiation reaches the earth's surface in amounts determined by the time of year, time of day, latitude, altitude, ozone levels, cloud cover, and atmospheric particulate matter (1). The UVA to UVB ratio is approximately 20:1, and at least two thirds of this UVA is long-wave UVA I (2). UVB is greatest during the summer. UVA is much more constant through the year (3). About 80% of UVB and 70% of UVA radiation are present between 10.00 a.m. and 2:00 p.m. (3).

UV radiation has acute and chronic effects on the skin. The epidermis mostly absorbs UVB. UVA penetrates more deeply into the skin, to the dermis. UV radiation generates reactive oxygen species (such as singlete oxygen, hydrogen peroxide and superoxide anion) that damage and destroy the skin (4). It is well documented that UV radiation causes sunburn, premature aging of the skin, skin cancers and cataracts, immunosuppression, and activation of latent viruses (5). Some of the acute and chronic effects of UV radiation are shown in Fig. 1 (6).

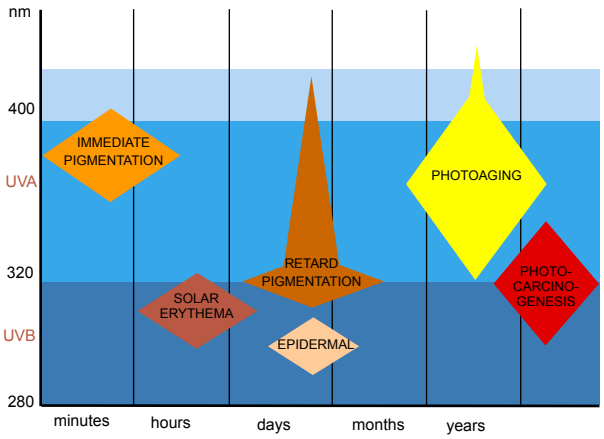

Figure 1. Acute and chronic skin effects of UV radiation (Self modification made after Jeanmougin M. Notions fondamentales de photobiologie cutanee. In: Jeanmougin M. Photodermatoses et photoprotection. Unite de Photobiologie Dermatologique, Hospital Saint-Louis, Paris, 1983;11-39.(6))

The measures that can be taken to achieve optimal sun protection include avoidance of sun exposure, use of photoprotective clothing, and application of broad-spectrum sunscreens. In recent years, scientists around the world have been developing novel agents and experimental modalities to minimize the harmful effects of UV radiation, such as antioxidants, alpha-MSH, polyphenol in green teas, genistein, NF-kB decoy oligodeoxynucleotides, pTpT vaccination and IL-12 (7).

SUNSCREENS

Sunscreens have become widely use for the prevention of short- and long-term sun damage. They are incorporated into a broader range of consumer products such as facial cosmetics, hair sprays and dyes, perfumes, shampoos, and shaving creams (8). They are regulated as drugs in the USA, Canada and Australia, and as cosmetics in Europe.

Mechanism of action

According to the mechanism of action, sunscreens are divided into two broad categories: chemical (organic) sunscreens and physical (inorganic) sunscreens or sunblockers.

Chemical sunscreens are agents that absorb specific photons of UV radiation with excitation to a higher energy state. They are generally aromatic compounds conjugated with an electron-releasing group para or ortho to an electron-acceptor group. These chemical structures absorb the UV photons causing delocalization of electrons from the electron-releasing to the electron-acceptor and move the molecule to a higher energy state. Later, the molecule returns to its basal state while emitting the energy that is lower in magnitude than the energy initially absorbed to cause the excitation (9) (Fig. 2).

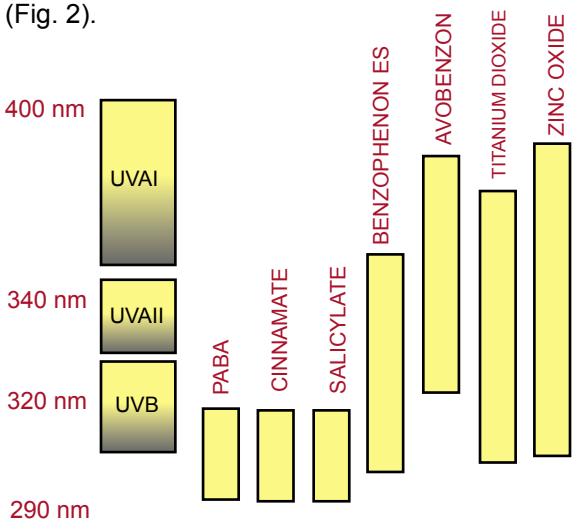

Figure 2. Chemical and physical sunscreens and their absorbtion spectra. Modified from: DeBuys HV, Levy SB, Murray JC, Madley DL, Pinnell SR. Modern approaches to photoprotection. Dermatol Clin 2000;18:577-90 (4), and Braun-Falco O, Plewig G, Wolff HH, Burgdorf WH. Sunscreens. In: Braun-Falco O, Plewig G, Wolff HH, Burgdorf WH, eds. Dermatology. 2nd ed. Berlin, Heidelberg: Springer-Verlag; 2000. p.1735-6. (11)

Chemical sunscreens are wavelength-selective with a specific absorption spectrum. Therefore, they are divided into UVB and UVA sunscreens. The UVB sunscreens are effective in absorbing the entire UVB spectrum. On the other hand, UVA sunscreens have a limited absorption spectrum, primarily absorbing shorter UVA II wavelengths (320-360 nm) (10).

The chemical sunscreens used today and their ranges are as follows: UVB sunscreens including cinnamates (290-320 nm; λmax 311 nm), salicylates (290-320 nm; λmax 307 nm), octocrylenes (290-320 nm; λmax 303 nm), enisilizoles (λmax 310 nm), camphor derivatives (λmax 300 nm); UVA sunscreens including butyl methoxydibenzoylmethane (avobenzone; Parsol 1789, 305-385 nm; λmax 358 nm), butyl tetraphthalydine dicamphor sulfonic acid (Mexoryl SX, λmax 345 nm); and UVA and UVB sunscreens including benzophenones (250-365 nm; λmax 288 or 325 nm) and

menthyl anthranilates (λmax 336 nm) (4,11).

Physical sunscreens create a barrier that reflects, scatters, or physically blocks UV light. They have been defined as opaque formulations, the effectiveness of which depends on the diameter or size of their particles and the thickness of the film to reflect or scatter UV radiation and visible light (12). The newer micro-sized forms of physical blockers are not just inert materials; they may also function in part by absorption. Physical sunscreens are categorized into chemicals that can scatter visible light and UV radiation equally well, scatter visible light and absorb UV radiation, or scatter and absorb visible light and UV radiation to a different extent (13). Titanium dioxide and zinc oxide in micro-sized forms can absorb UV as well as scatter and reflect visible light and UV radiation (13). Titanium dioxide and zinc oxide protect against UV light from 250 to 340 nm, but protection against UVA1 is statistically superior for zinc oxide (340 to 380 nm) (14).

Sun protection factor and UVA protection methods

Sun protection factor (SPF) is a laboratory-derived effectiveness number of the sunscreen preparation. The concept of SPF was originally proposed by the Austrian scientist Franz Greiter (15). SPF is defined as the dose of UV radiation required to produce 1 minimal erythema dose (MED) on sunscreen-protected skin divided by the dose of UV radiation required to produce 1 MED on unprotected skin. Based on this definition, for example, an individual who burns after 20 minutes of sun exposure can extend the period of time until the burn begins at one hour with SPF 3.

The proposed sunscreen evaluation guidelines include a detailed and very accurate protocol determined in a number of tested subjects, their skin type (types I, II, III according to Fitzpatrick), the site of testing (i.e. lower back), the source of light, and the method of reading the results and calculating the final SPF (9). The standard method of SPF testing involves a sunscreen application of 2 mg/cm^2 with a gloved finger. Several recent studies have shown that most persons apply only 20% to 60% of the amount of sunscreen (0.5-1.0 mg/cm^2) used to measure SPF, therefore the SPF measured in the laboratory may be as much as 30% to 50% of the measurements obtained in sunlight (16,17).

The SPF is based on the measurements of photoprotection against erythema induced by UVB radiation. Higher SPF product allows individuals to spend greater amounts of time in the sun without burning and allowing exposure to the high doses of UVA. There is no exact protocol for testing UVA protection. The methods of UVA protection available are shown in Table 1 (4). *In vivo* methods include immediate pigment darkening, persistent pigment darkening, protection factor in UVA determination, and erythema induced after topical psoralens application and UVA exposure (18-23). The critical wavelength determination is an *in vitro* method for testing UVA protection (20,24). A detailed discussion is beyond the scope of this article. Each method has its own limitations and indications for a particular clinical situation and skin type. The American Academy of Dermatology Consensus Conference on UVA Protection of Sunscreens recommends the critical wavelength method as a criterion for broad-spectrum claim. The threshold should be 370 nm (20). This method should be combined with an *in vivo* method (20).

Table 1. UVA protection methods

Method	Endpoint	Indication
UVA protection factor (SPF)	Erythema	UV-A II
UVA protection factor	Erythema	UV-A II Skin phototypes I and II
Persistent pigment darkening	Delayed pigment darkening	Full UV-A Skin phototypes III and IV
Phototoxic protection factor	Erythema with topical photosensitizer	Full UV-A photosensitivity
Photosensitivity disease study	Flare in disease process	Specific photosensitivity diseases
In vitro	Transmittance through substrate (such as thin film)	Screening materials Convenient and practical

Adapted with courtesy from: DeBuys HV, Levy SB, Murray JC, Madley DL, Pinnell SR. Modern approaches to photoprotection. Dermatol Clin 2000;18:577-90 (4).

Vehicle

The vehicle is significant for determining sunscreen efficacy and cosmetic effect. It determines whether a sunscreen remains effective under general use conditions such as swimming and sweating (10). Lotions and creams are the first choice for most individuals. Gels penetrate better and offer a more rapid protection but have a greater potential of irritation, especially in the eye region. Sticks are more difficult to apply but are useful for protection of limited areas such as lips, nose and around the eyes. Aerosols are cosmetically elegant and rapidly cover wide areas (4,11).

Sunscreens are classified according to their resistance to water or waterproof qualities (10). A water-resistant product maintains the SPF level after 40 minutes of water immersion, whereas a very water-resistant or water-proof product should show the same SPF after 80 minutes of water immersion (25).

Adverse reactions to sunscreens

Adverse reactions to sunscreens are relatively rare and include subjective (sensory) irritation, contact urticaria, contact dermatitis, both irritant and allergic as well as phototoxic and photoallergic reactions.

Subjective (sensory) irritation, cosmetic intolerance syndrome, or status cosmeticus (26) are the most frequently reported adverse reactions to sunscreens (27). The reactions are described as stinging, burning or itching without visible skin signs, occurring within 30 to 60 minutes of cutaneous exposure (28) and disappearing within 2 hours or sometimes a few of days of exposure (27). Such reactions can be explained as biochemical irritation in a sensitive skin (27). The reaction usually occurs on the face, especially around the eyes.

Contact urticaria to sunscreens can be immune (type I immediate hypersensitivity) or non-immune (29). It is less common than contact dermatitis (30). Individuals with contact urticaria to sun-screening products describe the sensation of burning, stinging, or itching with redness or urticaria shortly after application of the product. Various methods have been used for testing patients for contact urticaria. For example, patch test to unaffected skin on the volar forearm for 15 to 20 minutes, then observing the test site after 45 minutes (30).

Contact and photocontact dermatitis, both allergic and irritant, can occur not only from the various sunscreening agents but also from the excipients such as emulsifiers, antioxidants and preservatives included in the formulation (28). Sometimes a patient will react to series of chemically related compounds (para-amino compounds). The use of sun-barrier (benzophenone) is associated with the risk of contact or photocontact allergic reactions (8). Cross-reactions occur between aniline dyes, sulfonamides, benzocaines and quinones, and phenothiazines. Sometimes a substance may be metabolized in the body so that the altered structure may show an unexpected cross allergy. Because of their mechanism of action and increasing use, chemical sunscreens have become one of the most common causes of photocontact dermatitis (31). PABA, oxybenzone, avobenzone and cinnamates are the most common senzitizers. During the ‘60ies, PABA was described as the leading cause of contact allergy among sunscreening agents (32). Its high sensitizing properties and carcinogenic potential (PABA can decompose to produce a nitrosamine degradation product) (33) were the causes for PABA being practically withdrawn from sunscreening products, so today most products are claimed as being “PABA-free”. PABA esters such as padimate O (octyl-dimethyl PABA) appear to be less sensitizing than PABA (28). Oxybenzone (benzophenone-3) has replaced PABA in sunscreening formulations, and it is the most common UV filter in cosmetics. Its increasing diffusion has led to oxybenzone to become the most commonly reported cause of sunscreen allergy today (34-38). The wider use of avobenzone (butylmethoxydibenzoylmethane or Parsol 1789) will probably cause a third “epidemic” of sunscreen allergy (39).

Physical sunblockers are not senzitizing, so excipients in a physical sunscreen should be suspected if such reactions occur (10).

Individuals with pre-existing eczematous conditions have a significant predisposition to develop sensitization because of their impaired cutaneous barrier (34).

Some authors suggest that sunscreening compounds should be tested in all cases of contact dermatitis in sunlight-exposed areas (40,41). Testing for sunscreen allergy includes patch, photopatch and scratch testing with all the ingredients in sunscreen formulations (chemical sunscreens, physical sunscreens and excipients included in formulations) (42,43). Photopatch testing is performed by applying nonirritating doses of potential photoallergens in duplicate sets on the intact skin of the back. One set is kept covered while the

other is exposed to 5-10 J/cm^2 of UVA radiation 24 hours later. The irradiated and nonirradiated sets are then compared 24 hours after light exposure. The diagnosis of contact allergy is made when the nonirradiated and irradiated areas are positive. The diagnosis of photocontact allergy is made when only the irradiated set shows positive reaction. When both sites are positive but the irradiated site shows stronger reaction than the nonirradiated site, contact allergy associated with photoallergy is diagnosed (43,44). The common allergic substances are chlorpromazine, musk ambrette, promethazine, benzophenone-3 and -10, PABA and octyl methoxycinnamate (Parsol MCX).

Physical sunscreens may be so occlusive that they can cause miliaria (28). Acneiform eruption to sunscreen products is rare (42). Some authors report that sunscreens could affect vitamin D synthesis causing measurable decreases in the synthesis of vitamin D3. Another report shows that regular use of sunscreens can reduce the level of circulating 25-hydroxyvitamin D (45,46). Marks *et al.* (47) found no significant difference in vitamin D levels between the sunscreen and placebo treated groups. Similar findings were recorded in the American sunscreen study using sunscreens with SPF 29 for a 2-year period (46).

Microfine zinc oxide (Z-Cote) is an effective transparent broad-spectrum photostable sunblock to attenuate UV radiation (UVR) including UVA1 (14). Zinc oxide is essentially insoluble. After application to intact and psoriatic skin, essentially unchanged serum zinc levels were measured (14). It is nonreactive, easy to formulate with other sunscreens, and can be readily used in daily care or in beach products including waterproof formulations.

The long-term use of a topical UVA/UVB sunscreen has been shown to contribute significantly to the prevention of photoaging and solar elastosis, decreased collagen content, nonspecific dermal inflammatory infiltrate, basement membrane abnormalities, increased glycosaminoglycan deposition, and epidermal thickening (48). The regular use of sunscreens (not only on the warmest days in summer) can significantly reduce cutaneous neoplasia by suppression of precancerous lesions (49).

Sunscreens (chemical and physical) by careful application of products at a surface density of 2 mg/cm^2 (SPF is conventionally determined) are effective in photoprotection (50). Diffey and Grice demonstrated that there was no statistically significant difference between the amounts of sunscreens applied by subjects of different skin types, yet there was a tendency for subjects with lower skin types to apply more sunscreen than those who burnt less easily (50). Several studies have suggested the lack of correlation between the sunscreen SPF and protection of the skin immune system, potentially allowing for greater damage to the skin by removing the natural protective erythemal response to sun exposure. Murine studies have demonstrated that sunscreens provide higher erythemal protection than the protection from the systemic or local cutaneous immune systems (51). Davenport *et al*. studied impairment of the epidermal alloantigen-presenting capacity due to UV radiation and the protection provided by six sunscreen creams in the human skin explant system (51). They proved that the creams tested in the study provided protection beyond their *in vitro* SPF values, and that the SPF obtained was highly UV wavelength specific but poorly correlated with SPF values *in vivo*. Future studies will encompass protection provided at DNA and protein levels in the explant system (51).

Sunscreen allergy is uncommon in the contact dermatitis clinic in Singapore (52). Out of 61 patients only 5 were found to have positive allergic reactions to 2-ethylhexyl-p-methoxycinnamate (Parsol MCX), mexenone, and oxybenzene. The authors conclude that the incidence may rise in the near future (52). Based on the 7-year experience of photopatch testing with sunscreens in Sweden (355 consecutive patients), benzophenone-3 (Eusolex 4360) was for the first time identified as the most common allergen, followed by isopropyl dibenzoylmethane (Eusolex 8020) and butyl methoxydibenzoylmethane (Parsol 1789). The authors pointed to the importance of including UV filters in the standard photopatch protocol (53). Zhang *et al*. report on erythema-multiforme-like eruption that appeared 10 days after photoallergic contact dermatitis due to an oxybenzone sunscreen cream (Deepan®). The patient's eruption persisted for some 20 days despite treatment with topical and systemic corticosteroids (54).

Photosensitive patients often comment that sunscreen products seem to be of little benefit. Azurdia *et al*. performed fluorescence measurement (spectroscopy) on all uncovered body areas (17 sites) after applying sunscreen in a manner they would normally do on a bright sunny day. The overall median sunscreen thickness was 0.5 mg/cm^2 with median thickness at different sites ranging from 0 to 1.2 mg/cm^2. As the efficacy of pho-

toprotection provided by a sunscreen depends on the amount applied, the SPF achieved in a clinical setting will be by far lower than the anticipated one, and photosensitive patients should be advised to use high SPF products (55).

Photocontact dermatitis due to sunscreens or other allergens is only rarely observed in children. Hence, Ferriols and Boniche have described photoallergic eczema caused by a chemical sunscreen in a 12-year-old girl, with cross-reactions to ketoprofen and oxybenzones (56). Using European Colipe Guidelines, Gabard and Ademola demonstrated the minimal erythemal dose (MED) of the lower lip to be higher than the back skin MED in fair-skinned people (57). The lipstick sunscreen effect measured on the lips was found to be lower than the one measured in the classic way on the skin of the back. This may be due to the adaptation of this particular anatomic location to continuous UVR exposure (57).

UV exposure causes cataract formation, sunburn, premature aging of the skin, activation of latent viruses, and immune suppression, which contribute to the development of skin cancer. Nghiem *et al*. suggest that sunlight may depress the protective effect of prior vaccination, and point to the need of UVA protection when designing sun protection strategies (58). UV exposure suppresses immune memory and elicitation of immune response to a common opportunistic pathogen (58-60).

In recent years, novel agents and experimental modalities with the potential to offer enhanced protective effects against deleterious sequels of sun exposure have been elucidated, e.g., antioxidants, alpha-MSH, polyphenol in green teas, genistein, NF-kB decoy oligodeoxynucleotides, pTpT vaccination, and IL-12 (61). As these new photo-protective tools are being developed by scientists around the world, greater effort is needed to promote sun protection awareness in the general public.

CONCLUSION

The use of sunscreens has increased steadily over the last decade as people become ever more aware of the harmful effects of UV radiation. The sunscreening ingredients have been incorporated in cosmetic products to prevent photoaging and the carcinogenic effect of solar radiation. As the result, allergy and photoallergy to UV filters are relatively rare but more frequent than in the past. Sensitization can develop to the various sunscreening agents and to the excipients in the formulations. It is concluded that sunscreening agents should be tested in all cases of contact dermatitis on the sunlight exposed areas, especially in patients with photodermatoses. It is important to note that using sunscreens does not allow for a prolonged sun exposure. Avoiding sun exposure, especially between 10.00 a.m. and 4:00 p.m., staying in shade, wearing protective clothing, broad hat and sunglasses, and regular use of broad-spectrum UVA and UVB sunscreens with at least SPF 15 remain the best and most desirable methods of sun protection.

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