Ultraviolet radiation protection: current available resources in photoprotection *

Proteção à radiação ultravioleta: recursos disponíveis na atualidade em fotoproteção

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Abstract: Ultraviolet radiation can damage the DNA, cause immunosuppression, chemical and histological alterations in the epidermis, early photoaging, cataracts and carcinogenesis, among others. Photoprotection prevents these and other harmful effects of ultraviolet radiation. Sunscreens, protective clothing, proper accessories and safe sun exposure are essential photoprotection tools. The main forms of photoprotection are presented and discussed in this article, including sunscreens containing organic and inorganic filters, the assessment of their efficacy and current developments on the topic.
Keywords: Protection; Radiation protection; Solar radiation; Sunscreening agents; Ultraviolet filters

Resumo: A radiação ultravioleta pode provocar danos ao DNA, imunossupressão, alterações químicas e histológicas na epiderme, envelhecimento precoce, cataratas e carcinogênese, dentre outras deteriorações. A fotoproteção previne estes e outros efeitos danosos da radiação ultravioleta. Protetores solares, vestimentas, acessórios adequados e exposição segura ao sol são ferramentas essenciais da fotoproteção. Neste artigo, são apresentadas e discutidas as principais formas de fotoproteção, incluindo os protetores solares com filtros inorgânicos e orgânicos, a avaliação da eficácia dos mesmos e atualizações envolvendo o tema.
Palavras-chave: Filtros ultravioletas; Proteção; Proteção radiológica; Protetores de raios solares; Radiação solar

INTRODUCTION

Sunlight is composed of a continuous spectrum of electromagnetic radiation which is divided and named according to the range of wavelengths (λ): ultraviolet (UV) (100-400nm), visible (400-780nm) and infrared (> 780 nm). These different ranges of λ, from solar radiation, radiate the Earth's surface and are distributed as follows: 56% of infrared, 39% of visible light and 5% of ultraviolet radiation. UV radiation corresponds to a restricted region of the electromagnetic spectrum and is traditionally subdivided into: UVC (100-290 nm), UVB (290-320 nm) and UVA (320-400 nm). UVA radiation, in its turn, is classified into UVA1 (340-400 nm) and UVA2 (320-340 nm).[1,2,3]

Upon reaching bare skin, UV radiation triggers a complex process associated with morphological and chemical reactions of cumulative action. There may be formation of reactive oxygen species, histochemical changes of varying severity, thickening of the stratum spinosum and flattening of dermoepidermal junction.[1,3,4,5,6]

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Several skin molecules can absorb UV radiation and undergo chemical changes due to this absorption. DNA is one of the major molecules that absorb UV radiation. It can undergo mutations that can later result in malignant cell transformation. UV radiation can activate components of the skin immune system, triggering an inflammatory response through different mechanisms such as direct activation of keratinocytes and other cells that release inflammatory mediators, and redistribution and release of sequestered autoantigens from cells damaged by UV radiation. [7]

According to Gonzales et al, 2008, photoprotection is a prophylactic and therapeutic element against the damaging effects of UV radiation. Photoprotection is achieved through the use of sunscreens, protective clothing and limited exposure to sunlight. The first line of defense against these harmful effects is the use of photoprotectors, also called sunscreens. They may be composed of various UV filters, including inorganic and organic filters. Inorganic filters are physical blockers and organic filters are chemical absorbers. Their effectiveness can be determined by *in vitro* and *in vivo* methods through the obtention of the sun protection factor (SPF) value and it is related to UVB radiation. [3.8 to 11]

In this article, we will address the damage caused by UV radiation to human skin and the different forms of photoprotection, including environmental photoprotection, photoprotection by clothing and accessories and the use of sunscreens.

ULTRAVIOLET RADIATION

UV radiation is absorbed by various chromophores in the skin, such as melanin, DNA, RNA, proteins, aromatic amino acids (e.g. tyrosine and tryptophan), urocanic acid, among others. The absorption of UV radiation by chromophores causes different photochemical reactions and secondary interactions, involving reactive oxygen species, and results in harmful effects when there is excessive exposure. [3]

DNA is a major target of UV radiation. Pyrimidines undergo photochemical changes, resulting in cyclobutane dimers and other byproducts that are physiologically repaired by specific enzymes. Excinuclease ABC, DNA polymerase I and DNA ligase are examples of enzymes involved in the DNA repair system. This system is effective, but excessive sun exposure can make repair less efficient. Therefore, the use of sunscreens is essential to reduce the harmful effects of UV radiation on genetic material. Photochemical reactions exert important effects on human skin, depending on λ and the amount of energy. The epidermis and dermis undergo chemical and histological changes after persistent sun exposure. These changes favor the rapid development of wrinkles, roughness, dryness, telangiectasias, uneven pigmentation, immunosuppression and lesions, which may be benign, premalignant or malignant. [3, 4.12]

UV radiation affects the eyes. Each year approximately 3 million people suffer from loss of vision due to damage related to UV radiation, such as cataracts and photoconjunctivitis. [3]

It is known that UV radiation has beneficial health effects. It stimulates production of vitamin D_3 (cholecalciferol), involved in bone metabolism and immune system functioning. It is also used to treat skin diseases like psoriasis and vitiligo. Regular exposure to UV radiation characterizes phototherapy, which can be used in combination with drugs that increase sensitivity to radiation, improving the symptoms of certain skin diseases. [1,3,4,5,6]

The effects of early skin aging are associated with UVA radiation. Such radiation has higher λ (> 320 nm) and lower energy. This range of λ favors penetration of this radiation into the dermis, negatively affecting the natural elasticity of the skin and aggravating photodermatoses such as lupus erythematosus and polymorphous light eruption. UVA radiation also causes a reduction in the number of Langerhans cells and increases the amount of inflammatory cells in the dermis. [1]

DNA damage, inflammation and carcinogenesis are characteristics associated with UVB radiation. Compared with UVA radiation, this type of radiation has lower wavelength and more energy. UVB radiation directly interacts with DNA to produce mutations in pyrimidine dimers that are linked to non-melanoma skin cancer (basal cell and squamous cell carcinoma). They can play an important role in some photodermatoses, such as polymorphous light eruption and solar urticaria, as these are sensitive to visible light and UV radiation. [1,4,13,14]

Infrared and visible light

The damaging effects of sunlight on human skin can not be attributed only to individual wavelengths. The interaction between different wavelength bands, such as visible light, UV radiation and infrared plays an important role in the development of these effects. [15]

Infrared radiation (IR) can transmit energy as heat, raising the temperature of the skin. Human skin exposed directly to IR can have its temperature raised to over 40 °C due to conversion of IR into heat. Chronic exposure to heat can cause changes in human skin and diseases such as erythema *ab igne*, characterized by reticulate erythema, hyperpigmentation, fine scaling, epidermal atrophy, and telangiectasias. [15.16]

Visible light and near infrared can induce pigmentation. An *in vivo* study was conducted to determine color changes that occur during irradiation. A polychromatic light source of 390 to 1700 nm that simulated the solar spectrum was used, but without UV radiation. It was found that pigmentation occurred even without the presence of UV radiation. Other studies have shown that exposure of normal skin to visible light can result in the induction of immediate pigmentation *(Immediate Pigment Darkening* - IPD), immediate erythema, and delayed tanning *(* DT). Visible light also contributes to the production of free radicals and thereby induces DNA damage indirectly.[17]

Environmental photoprotection

Several environmental factors influence the intensity of the UV radiation that reaches the Earth's surface. Ozone levels, height and cloud cover, environmental pollutants and seasons of the year are examples of these factors. The ozone layer absorbs 100% of UVC radiation, 90% of UVB radiation and it hardly absorbs UVA radiation. UV radiation not absorbed by ozone may, in contact with water, penetrate it in the rate of 80%. Water does not reflect UV radiation, so this radiation penetrates the water. UV radiation can be reflected under other conditions. Snow and sand allow UVB radiation to be reflected and snow can reflect UVB radiation at a rate of 85%.[1]

Ozone (O_3) is a molecule capable of photoabsorption. It is present in the stratosphere, its concentration naturally varies according to temperature, time, latitude and altitude. Starting in the 70s, the level of stratospheric ozone began to decline annually. This decrease was particularly significant in the Southern hemisphere. This occurred mainly due to the use of substances that can damage the ozone layer, such as chlorofluorocarbons. These substances undergo photolytic dissociation upon reaching the stratosphere, releasing chlorine atoms. Chlorine reacts with the ozone molecule, resulting in oxygen and chlorine monoxide.[13.18]

Reduced levels of ozone cause an increase in the amount of UV radiation that reaches the Earth. It is estimated that for every 1% decrease in ozone levels, there is an increase of 1 to 2% in the amount of UVB radiation reaching the Earth's surface. When we associate this fact with the biological amplification factor (increased incidence of skin cancer due to increased UVB radiation), we verify that for every 1% decrease in ozone level, the quantitative risk of developing skin cancer increases by 3 to 4.6% for squamous cell carcinoma and 1.7 to 2.7% for basal cell carcinoma. Stabilization of the levels of stratospheric ozone has been recently observed, probably due to the measures adopted by some countries in order to reduce the emission of substances that can damage the ozone layer.[13.19]

Photoprotection by clothing and accessories

Clothing, sunglasses and hats are easily available and effective approaches for protecting the body against the harmful effects of UV radiation. The American Academy of Dermatology recommends the use of appropriate clothing and sunglasses for prolonged sun exposure, but some types of fabric do not provide sufficient protection. [1,3,14,20]

Several factors influence the photoprotection offered by fabrics. In general, fabrics made of tightly woven fibers, thicker, more rigid and darker best protect the body, as compared with those made of loosely woven fibers, thinner and less rigid. Therefore, stiffness, color, thickness and weight of the fabric all influence its capacity of photoprotection.[1,13,21]

The ultraviolet protection factor (UPF) assesses the degree of protection offered by clothing. It is similar to the sun protection factor (SPF) used for sunscreens; however, it supposedly offers protection against both UVA and UVB radiation, a characteristic that is absent in the SPF, which offers UVB protection only. [13.14]

The UPF relates the time of safe (protected) sun exposure to exposure time without protection, so the actual protection offered by clothing can be determined. This is an *in vitro* methodology related to the assessment of UV radiation transmission through fabrics. This factor varies according to the type, color, texture, stiffness and moisture of fabrics. It also varies based on the methods involved in the manufacture of clothing and accessories made of these materials. According to the European Committee for Standardization, the UPF value must be higher than 40 and the UVA transmission rate should be inferior to 5% for the fabric to offer adequate photoprotection. However, the Australian Standard advocates a value of more than 15 UPF.[1,3,13,14,21]

New fabrics are currently capable of offering high sun protection. Some new fabrics contain titanium dioxide particles dispersed among their fibers, allowing combined UVA and UVB protection. The incorporation of particles of inorganic sunscreens increases the UPF value. Classic fabrics such as cotton may also have their UPF value increased with the addition of sunscreens. [14]

In addition to clothing, other accessories are equally important for photoprotection, such as sunglasses, gloves, caps and hats. Hats are useful for protecting the scalp, ears, hair, eyes, forehead and neck, in addition to providing shade for the face, which can protect the cheeks, nose and chin. The effectiveness of the protection offered by a hat or cap is related to the size of its brim, as well as the material used in its manufacturing. Hats with a wide brim reduce the eye surface exposed to UV radiation by 50%. Those with a brim of at least 4 cm protect the back of the neck. Gloves are useful for preventing the signs of photoaging of the hands, such as spots on their surface [1,3,14,22]

Sunglasses prevent eye damage caused by UV radiation, such as cataracts, photoconjunctivitis and progressive loss of vision. There should be protection against UV radiation and visible light and they must cover the lateral vision field. Some factors influence this protection: size, shape, ability to block UV radiation and anti-reflection coating of the back of the lens.[1,3,14]

It is advisable that sunglasses have lenses with side shields, be of gray or neutral color, have good optical quality and transmittance of visible light that is suitable for visual comfort. The FDA *(Food and Drug Administration)* has set parameters for sunglasses. Permittivity must be less than 0.001% for wavelengths between 200 and 320 nm and less than 0.01% for wavelengths between 320 and 400 mm. The American Academy of Ophthalmology recommends that the glasses filter out 99% of UV radiation and that the lenses do not transmit more than 1% of UVA and 1% of UVB. [1,3,14,22]

Photoprotectors

The use of sunscreens is the main cosmetic approach against the harmful effects of UV radiation. Many studies show that regular and proper use of photoprotectors reduces the number of cases of actinic keratosis, squamous cell carcinoma and attenuates the development of new nevi in children. Moreover, the regular use of photoprotectors prevents premature skin aging.[1,3,13,14]

Sunscreens are cosmetic preparations that have various presentation forms. They can be found in the form of hydroalcoholic lotions, oils, oily gels, oil in water emulsions (O/A), water in oil emulsions (W/O), sunscreen sticks and sprays, among others. Hydroalcoholic lotions usually offer reduced protection with irregular formation of a protective film. They may also cause skin dryness. Oils offer superior protection as compared to hydroalcoholic lotions, but they do not reach a high SPF value. Oily gels have an oleaginous gel composition, offering superior protection as compared to fluids. Emulsions offer the best protection. Sunscreen sticks are used in lip formulations and aerosols in hair formulations, for example.

Sunscreens contain filters that are molecules or molecular complexes that can absorb, reflect or scatter UV radiation. The first sunscreens were marketed in 1928. Very differently from current formulations, the first sunscreen was composed of a combination of benzyl salicylate and benzyl cinnamate. In World War II, soldiers assigned to areas of tropical climate, in order to avoid sunburn, used red veterinary petrolatum, PABA (4-aminobenzoic acid) and p-dimethylaminobenzoic acids.[1,3,13,14]

The FDA began to regulate the development of photoprotectors in the 40s. This agency currently regulates the use of sunscreens. Table 1 describes the sunscreens approved for use in the USA, in accordance with the International Nomenclature of Cosmetic Ingredients (INCI) and the Chemical Nomenclature. [1,3,13,14, 23.24]

The European Community allows the use of 27 different UV filters in cosmetic formulations and Australia, 28. These numbers contrast with those in Chart 1, which shows the number of approved filters to be lower than the the numbers in Europe and Australia. Since 1978, the FDA has only allowed the addition of three new UV filters to the list. The regulatory approval process of new filters in the U.S. is time consuming because filters are treated as over-the-counter (OTC) products. However, in Europe and other locations, the regulatory approval process is faster, since sunscreens are considered cosmetics by regulatory agencies. In the 70s, PABA became the main active compound in highly effective comercialized sunscreens. In the following two decades, attention turned to the formulation of photoprotectors to raise the FPS of those already available in the market with the addition of new sunscreens. Currently, given the damage that UVA radiation causes, the development of photoprotectors aims to create products that offer UVA and UVB protection. [1,13,14]

Efficacy

The effectiveness of a sunscreen can be determined by *in vitro* and *in vivo* methods. The FPS can be defined as the ratio between the minimal erythematous dose (MED) of skin protected with the sunscreen under study and MED of unprotected skin. The MED is the amount of effective energy, expressed in Joules/cm^2, required for the production of the first noticeable erythematous reaction with well-demarcated borders, identified by a trained and qualified professional.[10.11]

Equation 1 mathematically determines the FPS value. For this, an *in vivo* methodology that meets the *Federal Register* - FDA norm - *May* 12, 1993 - *Sunscreen Drug Product for Over the Counter Human Use,* or the Colipa Norm - *Colipa Sun Protection Factor Test Method - October* 1994, according to the RDC resolution number 237/02 of August 22, 2002 is advocated in Brazil.[25]

MED = minimum amount of radiation capable of causing minimal erythema

Chart 1: List of FDA-approved filters

Organic		Inorganic
UVA INCI/Chemical substances	**UVB INCI/Chemical substances**	**UVA/UVB INCI/Chemical substances**
1-(4-TERT-BUTYLPHENYL)-3-(4-METHOXYPHENYL) PROPANE-1,3 DIONE/ Avobenzone	4-Aminobenzoic acid [PABA]	TITANIUM DIOXIDE
MENTHYL ANTHRANILATE	OCTYL (or ETHYLHEXYL) DIMETHYL PABA/ 2-ethylhexyl 4-dimethylaminobenzoate	ZINC OXIDE
BENZOPHENONE-8/ 2,2' dihydroxy-4 –methoxybenzophenone	homomenthyl salicylate	
BENZOPHENONE-3/ 2 hydroxy-4 -methoxybenzophenone (oxybenzone)	2-ETHYLHEXYL SALICYLATE	
BENZOPHENONE-4/ - 2-Hydroxy-4-methoxybenzophenone-5-sulphonic acid and its sodium salt	TEA-SALICYLATE/ TRIETHANOLAMINE SALICYLATE	
TEREPHTHALYLIDENE DICAMPHOR SULFONIC ACID/ 3,3`- (1,4-Phenylenedimethylene)-bis (7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-ylmethanesulphonic acid) and its salts	CINOXATE/ 2-ethoxyethyl 4-methoxycinnamate	
	OCTYL METHOXYCINNAMATE/ – 2 ethylhexyl 4-methoxycinnamate	
	OCTOCRYLENE/ 2 - Cyano - 3,3`- 2 – ethylhexyl diphenylacrylate	
	PHENYLBENZIMIDAZOLE SULFONIC ACID/ 2- phenylbenzimidazole- 5-sulfonic acid and its potassium, sodium and triethanolamine salts	

FDA: Food and Drug Administration; INCI: International Nomenclature of Cosmetic Ingredients

FPS = MED (protected skin)
MED (unprotected skin)

Equation 1 - Determination of Sun Protection Factor

Alternative *in vitro* assays have been developed, such as spectrophotometric tests. They are based on the analysis of spectral absorption or UV radiation transmission of solutions of photoprotectors diluted in appropriate solvent (e.g. absolute ethanol) or on the determination of the transmission spectrum or reflection obtained in reflectance spectrophotometer (spectrophotometric FPS through film). In this case, there is no need to obtain samples of solutions, and inorganic filters can be evaluated.[26,27,28]

There are specific methods to assess UVA protection, such as the calculation of FPA-PPD *(Persistent Pigment Darkening)*. This method is based on the response of persistent pigmentation to UVA radiation. It is an *in vivo* method that evaluates the response of the skin to pigmentation after exposure (from 2 to 4 hours) to UVA radiation. Another *in vivo* method involves the calculation of the IPD *(Immediate Pigment Darkening)*, that is, transient darkening of the skin after exposure to UVA radiation. [29,30]

The FDA proposed to include a rating system for UVA protection rate. This system is gradual and uses stars to rate the degree of protection, so UVA protection is classified into low, average, high or very high according to the number of stars. Low protection against UVA radiation is represented by a star, average protection by two stars, high protection by three and very high protection by four stars. This classification system depends on *in vitro* and *in vivo* results of tests for UVA protection. [31]

According to the FDA, two tests are needed to assess UVA protection. One evaluates the ability of a sunscreen to reduce the penetration of UVA radiation; the other determines the capacity of the product to prevent tanning. The test indicating the lowest UVA protection offered by the product will indicate the number of stars corresponding to this product. This methodology allows the consumer to obtain information about the UVB protection offered by the product, through indication of the FPS value and also UVA protection, according to a graduated scale of stars.[31]

The response to PPD *(Persistent Pigment Darkening)* was selected to develop an *in vivo* standard protocol. The results obtained with this protocol demonstrated reproducibility for a wide range of products and levels of UVA protection. In 1996, the Japan Cosmetic Industry Association adopted the PPD method to assess the effectiveness of UVA protection offered by photoprotectors. In 2001, Korea followed suit and in 2007, China also adopted the method as their standard.[32]

The European Commission recommended the use of the method in 2006 and the FDA has recently proposed an amendment to the method in the sunscreen monography. The method is currently in the process of standardization by the International Standardization Organization (ISO).[32]

In Brazil, there is no standardized methodology for the determination of UVA protection. The ANVISA Resolution 237, of August 22, 2002, only mentions that UVA protection should be measured by means of recognized methodologies that have been properly validated.[33]

Inorganic filters

Zinc oxide, titanium dioxide, iron oxide, red veterinary petrolatum, talc, calamine, and kaolin are examples of sunscreens that reflect and scatter UV radiation and visible light by means of an opaque barrier formed by a particle film on the skin. Depending on particle size, protection can occur not only through reflection but also absorption. Inorganic blockers show relative stability, do not react with organic filters and are often clinically safer. Thus, they are considered nontoxic, stable and the first choice of sunscreen for patients with a history of allergy. However, according to Cosmetic Science, they may have drawbacks such as the development of an opaque white color on the skin after application, promoting the development of comedogenesis and transfer to clothing, with consequent reduction of the photoprotection.[1,3,13]

The enhancement of photoprotectors with inorganic filters occurred in the early 90s, when micronized forms with titanium dioxide and zinc oxide were developed. Pharmaceutical development has also been responsible for their encapsulated forms, through the use of polymers. The original size of particles corresponded to the range of 100 to 300 nm; with their micronization, they were reduced to 10-50 nm, corresponding to 50-90% of their original size. As a result, photoprotectors with inorganic filters had higher acceptability because they enabled the development of formulations which, after application, became transparent. Despite reduction in particle size, they still offered high protection against UV radiation and significant UVA protection.[1,13,14]

Titanium dioxide and zinc oxide have similar characteristics and offer UVA protection. However, zinc oxide offers better protection. They do not show significant skin irritating properties or sensitization potential. *In vivo* and *in vitro* studies do not show the penetration of titanium dioxide but, in relation to zinc oxide, research has indicated limited penetration into the skin. Micronized forms of titanium dioxide and zinc oxide can undergo photochemical reactions that jeopardize their effectiveness, causing damage to genetic material or changing cell homeostasis. The coating of particles with dimethicone or silica promotes their stability, reducing such drawbacks.[3,13,14]

New developments have recently surfaced to raise the quality of inorganic photoprotectors; for example, their encapsulation with carnauba wax. Carnauba wax contains cinnamates which, together with titanium dioxide, generate stable dispersion with proper viscosity and a significant increase in both the SPF value and UVA protection.[3.13]

Organic Filters

Organic filters are molecules capable of absorbing UV radiation and transforming it into energy that is harmless to humans. Graphs 1 and 2 show the absorption spectrum of two organic filters.[9]

They are essentially aromatic compounds combined with carboxylic groups which often have an electron donor group such as, for instance, an amine or methoxyl in the *ortho* or *para* position of the aromatic ring. As for solubility, they may be water or fat soluble. The mechanism of action of organic filters involves the absorption of UV radiation followed by the excitement of the π HOMO orbital (occupied molecular orbital of higher energy) to the π * LUMO orbital (unoccupied molecular orbital of lowest energy). These molecules, upon returning to their ground states, release excess energy absorbed in the form of heat, for example.[8,9]

These molecules are divided into UVA filters, which offer protection against UVA; UVB filters, which offer protection against UVB radiation, and broad-spectrum filters, which provide protection against UVA and UVB. UVB filters are effective; they can filter out 90% of UVB radiation and have been widely used for decades. However, UVA and broad-spectrum filters are the result of recent research. Many products currently use a different combination of filters to obtain broad-spectrum protection. The effectiveness of organic filters is directly related to photochemical stability, easier and permanent dispersion and dissolution, and to water-resistance. These filters must be nontoxic and must not cause irritation or allergy.[3, 13]

UVB Filters

UVB filters absorb approximately 90% of the radiation of λ between 290 to 320 nm. PABA (4-aminobenzoic acid) was the first UV filter used and one of the first FDA-approved. Photoallergic reactions caused by this substance affect more than 4% of the population. Reactions with other *p*-molecules may occur and there is the possibility of carcinogenesis related to the use of products containing PABA. The first PABA-free products were developed in the 80s. PABA esters were marketed, which had advantages such as reduced reactivity and allergenicity. The only FDA-approved ester is Padimate O or octyl dimethyl PABA (2-ethylhexyl 4-dimethylaminobenzoate), most currently used in products to protect the hair and in combination with other filters to increase the SPF of sunscreens.[1,3]

Cinnamates are the most popular UVB filters in Europe and the U.S.; however, they have reduced substantivity and are often combined with other filters. They have lower potential to cause skin irritability. 2-ethylhexyl 4-methoxycinnamate is an example of this group of UVB filters. This UVB filter is the most powerful, capable of absorbing radiation of λ between 270-328 nm. Studies show that its nanoencapsulation with *poly-D, L-lactide-co-glycolide* results in decreased photodegradation.[1,3,13]

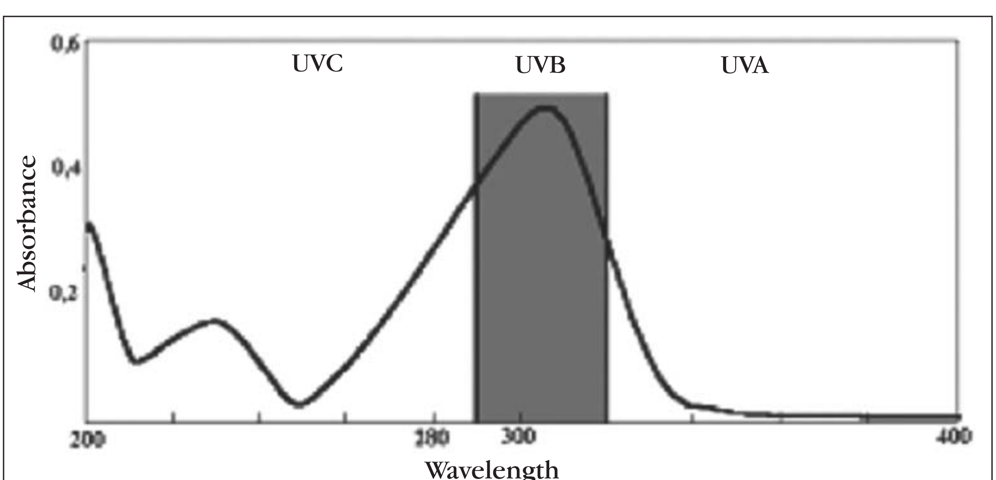
Salicylates are stable and safe aromatic compounds, water-insoluble, which have high substantivity. This group of compounds has been used as sunscreen for decades and also as solvents for poorly soluble sunscreens, such as benzophenones. We may cite 2-ethylhexyl salicylate, homomenthyl salicylate and triethanolamine salicylate. 2-ethylhexyl salicylate and triethanolamine salicylate are associated with the photo-induction of skin reactions. This does not occur with homomenthyl salicylate. Salicylates offer UVB protection in the range of 290-315 nm. Triethanolamine salicylate is more often used in products for hair protection.[1,3]

UVA Filters

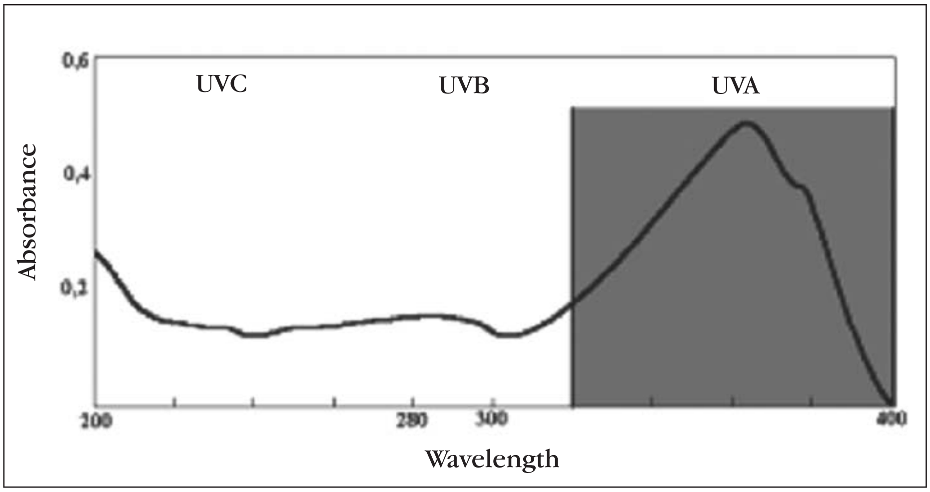
The main organic UVA filters in sunscreens include benzophenones (mainly oxybenzone), avobenzone, terephthalylidene dicamphor sulfonic acid, drometrizole trisiloxane, methylene-bis-benzotriazolyl tetramethylbutylphenol and bis-ethylhexyloxyphenol methoxyphenyl triazine. According to Baron et al, the FDA recently approved the use of terephthalylidene dicamphor sulfonic acid; however, methylene-bis-benzotriazolyl tetramethylbutylphenol and bis-ethylhexyloxyphenol methoxyphenyl triazine have not yet been approved by this agency. Menthyl anthranilate is classified as an UVA filter, but it is rarely used.[3.14]

Benzophenones are aromatic ketones, and the FDA approved the use of oxybenzone (benzophenone-3) in the early 80ss. This filter absorbs radiation in the wavelength range of 270 to 350 nm, covering UVB and UVA2 radiation. Benzophenones, as a class, are considered allergenic sunscreens. They have low substantivity and the incidence of contact and photocontact dermatitis is high.[1]

Avobenzone was introduced in the late 80s and early 90s. This UVA filter has revolutionized protection against UVA radiation. It was the first to provide UVA-I protection, covering the wavelength



Graph 1: Absorption spectrum of the filter 2-ethyl hexyl *p*-methoxycinnamate, 5.16 mg L in ethanol



GRAPH 2: Absorption spectrum of the filter 1-(4-terc-butylphenyl)-3-(4-methoxyphenyl) -1,2-propane dione, 5.20 mg L1 in ethanol

range of 310 to 400 nm. Avonbenzone suffers significant degradation as a result of exposure to light. Only 60 minutes of exposure to UV radiation reduce the effectiveness of the product by 50% to 90%, so the photostabilization of formulations becomes necessary. A sunscreen with good UVB protection is generally added, such as homomenthyl salicylate .[1,14,31]

Recent research aims at developing new vehicles for avonbenzone containing more effective stabilizers. Industries invest in the development of final formulations, involving, for example, combinations of avobenzone with octocrylene (2-cyano-3, 2-ethylhexyl 3-diphenylacrylate). The addition of *bis-ethylhexyloxyphenol methoxyphenyl triazine* photostabilizes avobenzone.[1,14,31]

Terephthalylidene dicamphor sulfonic acid was approved by the FDA in 2006. This filter was developed by L'Oréal ®, and patented in 1982. It is a photostable organic filter that absorbs the wavelength range between 290 and 390 nm, with maximum absorption peak at 345 nm. When it is combined with avobenzone, UVA protection is increased. *In vivo* studies have shown protection against photoaging and the development of photodermatoses.[1,14,31]

Another organic filter recently introduced in the market is drometrizole trisiloxane. In 2006, this filter was introduced in Canada; however, it has not been approved by the FDA. Drometrizole trisiloxane absorbs UVB and UVA-II and, in combination with terephthalylidene dicamphor sulfonic acid, has increased ability of UVA protection. [3,31]

Methylene-bis-benzotriazolyl tetramethylbutylphenol and bis-ethylhexyloxyphenol methoxyphenyl triazine are organic filters of broad-spectrum not yet approved by the FDA. Bis-ethylhexyloxyphenol methoxyphenyl triazine increases the photostability of avobenzone and both methylene-bis-benzotriazolyl tetramethylbutylphenol and bis-ethylhexyloxyphenol methoxyphenyl triazine act as active compounds in the prevention of photoaging.[3,31]

Antioxidants

The natural consumption of oxygen by aerobic beings generates oxidative processes. Under normal conditions, the human body is able to neutralize, by means of antioxidant systems, reactive oxygen species (ROS) generated physiologically, but in pathological conditions or under the effects of chronic and excessive exposure to UV radiation, an imbalance between the production of ROS and antioxidant systems is established. Therefore, there is an oxidative stress capable of causing skin cell damage, such as lipid peroxidation, protein denaturation and DNA changes. The damage caused may result in immunosuppression, premature skin aging and skin cancer development.[34,35]

Antioxidants are defined as substances which, when present in low concentrations as compared with those of an oxidizable substrate, significantly reduce or prevent the oxidation of this substrate. They may act by preventing the formation of free radicals, repairing the damage caused by them or sequestering them. Many cosmetic products on the market have built-in antioxidants to fight the signs of aging skin. Several studies currently investigate the action of antioxidants in photoprotection. Some studies evaluate their action in the prevention of skin erythema by determining FPS value and others evaluate their protective effects against molecular damage caused by oxidative stress induced by UV radiation. [34,36]

Polyphenols are natural components of plants that are found in fruit, vegetables, seeds, bark and flowers. They have antioxidant, anti-inflammatory and immunomodulatory properties. They are explored as chemopreventive agents in various skin diseases, including skin cancer. Studies have shown the effectiveness of natural polyphenols against inflammation, oxidative stress, DNA damage and suppression of the immune response induced by UV radiation. These protective effects contribute to their anti-photocarcinogenic action.[35]

Sunscreen controversy

Sunscreens have several health benefits, but there are controversies and challenges associated with the efficacy and safety of their use [3,12]

Allergy

According to Gonzalez et al, 2008, the exposure of the population to organic filters increased after they were added to various cosmetic products. A study of 603 Australian volunteers showed that 18.9% of the individuals using broad-spectrum sunscreen with SPF 15 or higher, for a period of seven months, showed signs of skin irritation. Allergic reactions to sunscreens were not found.

Allergic reactions to sunscreens and allergic contact and photocontact dermatitis are rare. Contact photoallergy usually occurs due to the presence of benzophenone-3 (oxybenzone), the major responsible for its development. PABA, amyl dimethyl PABA and benzophenone-10, well-known photoallergenic agents, are no longer used, contributing thus to reduce cases of skin irritation caused by the continuous use of sunscreens.[3,13,37]

Systemic absorption

UV filters, such as benzophenones and 2-ethylhexyl 4-methoxycinnamate, can be detected in plasma and urine of individuals who used them topically. However, most studies related to this were conducted with formulations having a high concentration of these substances, differently from the concentration found in commercially available products. In Brazil, ANVISA regulates the use and concentration of sunscreens in photoprotective formulations. Resolution 47 of 2006 lists the sunscreens that have been approved for use and their maximum concentration. Therefore, research on the systemic absorption of sunscreens must be conducted with formulations having the maximum concentration of sunscreens allowed by responsible agencies.[3,24,31]

Factors involved in the systemic absorption and chronic toxicity of UV filters have been intensely debated, but it is necessary to investigate the commercially available sunscreens to assess the degree of absorption of UV filters and the consequences of this absorption. [3,31]

***Synthesis of Vitamin D* (Calciferol)**

Ultraviolet radiation is necessary for the synthesis of vitamin D (calciferol). This synthesis occurs in the presence of UVB radiation. Photoprotectors are often effective in their UVB protection. Few studies associating the role of vitamin D, sun exposure and cancer prevention have been conducted, so research in this area is necessary. It is also important to investigate oral vitamin D and its synthesis after sun exposure. Studies about the optimal amount of vitamin D needed for its beneficial effects are also important.[31]

In 2007, the Canadian Cancer Society recommended that Canadian adults consider the daily intake of 1000 IU of vitamin D. This recommendation was based on evidence suggesting that vitamin D could reduce the risks of breast, prostate and colorectal cancer. Physicians should individualize sun protection, evaluating whether or not oral supplementation of vitamin D is necessary in each case and also the degree of photoprotection indicated for each patient.[31]

Nanoparticles

Currently, there is increasing use of nanomaterials in electronic components, antifungal and antimicrobial preparations, cosmetics, among others. Nanoparticles are unique particles with a diameter inferior to 100 nm that represent a subset of nanomaterials; their clusters can have sizes greater than 100 nm. Insoluble nanoparticles with diameters between 50 and 200 nm, mainly represented by titanium dioxide (TiO_2) and zinc oxide (ZnO) are used in photoprotectors. The reflection of UV radiation by TiO_2 is more efficient in particles sized between 60 and 120 nm. ZnO is commonly used in particles sized between 30 and 200 nm. The use of nanoparticles in photoprotectors improved the whitish appearance of traditional photoprotectors and created a more transparent vehicle, less viscous and with better spreadability on the skin. This improved its acceptability by consumers.[38,39]

The potential toxicity of nanoparticles in photoprotectors is the result of their size, the ability to escape immune defense mechanisms, the ability to form protein complexes, and most importantly, the ability to induce the formation of free radicals. [39]

Some review studies suggest a potential of penetration of nanoparticles topically applied to human skin causing systemic risk to health. They also suggest that nanoparticles can penetrate the skin and be distributed throughout the body by the circulatory system. The penetration of materials in the stratum corneum is limited by molecular size. The intercellular space between cells of the stratum corneum is approximately 100 nm[3] and it can be extended with the topical application of various products. This fact instigates debates about the penetration of nanoparticles into the stratum corneum. A study conducted by Philip et al, 2009, assessed the location and the possibility of penetration of nanoparticles dispersed in three photoprotectors, into normal and altered skin. They found that levels of TiO_2 and ZnO nanoparticles were nonexistent or very low to be detected in the layers of viable epidermis below the stratum corneum. This result cannot be extended to other photoprotectors, since different formulations may have different properties.[38,39,40]

Further studies should be conducted to determine the safety of TiO_2 and ZnO nanoparticles in sunscreens. In addition to the evaluation of skin penetration, assays of the generation of reactive oxygen species as a result of exposure of nanoparticles to UV radiation and the consequent penetration of ROS generated in the stratum corneum should be conducted.

CONCLUSION

The need for photoprotection is an irrefutable reality, whether for therapeutic and prophylactic action against premature aging or to decrease the incidence of skin cancer. Over the years, we have seen improvements in the development of photoprotectors to obtain safe and effective formulations which provide broad UV protection. Research studies related to the development of new molecules, less allergenic and with better photostabilization, are needed to obtain ideal photoprotectors.

In-depth studies of the safety, efficacy and systemic absorption of photoprotectors are important for the total understanding of the interactions involved in their use, which is essential and indispensable considering the damage caused by UV radiation. ❑

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