CHAPTER 12

Sunscreens

Guido Bens*

Ultraviolet Radiation

Naturally occurring ultraviolet radiation (UVR) from the sun has been divided into two broad band regions: low-energy UVA (with wavelengths of 320 to 400 nm) and high-energy UVB (280-320 nm). Relative effectiveness of different wavelengths in producing a biologic reaction is called action spectrum for this particular reaction. The most obvious acute reaction of white skin to UVR is erythema which is commonly addressed to as "sunburn". The action spectrum of solar erythema lies mainly in the UVB band region, with a peak at 295 nm and rapid decline towards the UVA region (Fig. 1): 295 nm UVB radiation (UVBR) is about 1000 times more erythemogenic than short-wave UVAR. Under normal conditions, middle and long-wave UVAR do not induce sunburn. UVAR has therefore been further broken down into two bands UVA1 (340-400 nm) and UVA2 (320-340 nm) because of the increased erythemogenic activity of UVA2 compared to UVA1.

Solar radiation is significantly modified by the earth's atmosphere with ozone in the stratosphere being the major photoprotective agent that absorbs all high-energy cosmic radiation, UVCR (200-280 nm) and short-wave UVBR up to 290 nm. Clouds, pollutants and fog furthermore decrease UVR by scattering and absorption. However, UVAR and visible light (400-700 nm) are much less affected by the way through the atmosphere. Less than 5% of the sunlight that reaches the earth's surface is UVR, with a ratio of UVA to UVB of about 20:1, depending on geographical latitude, altitude, season of the year, time of day and meteorological conditions.[1] UVAR but not UVBR traverses window glass and is therefore present also indoor. UV exposure does not only occur by direct sunshine on the skin, but also by light reflection, e.g., by snow, glass, sand and light-colored metals, with once more wavelengths in the UVA band being more reflected than UVBR. About 50% of effective UVA exposure has been estimated to occur in the shade.[2] The predominance of UVA in the solar energy in our environment permits UVA to play a far more important role in contributing to the harmful effects of sun exposure than previously suspected.

Effects of Ultraviolet Radiation in Human Skin

UVA penetrates far deeper into the skin than UVB does (Fig. 2): The major part (70%) of UVB is absorbed or scattered by the stratum corneum. Twenty percent of UVB reaches living cells in the epidermal spinous layer and 10% superficial dermis. UVAR and visible light are less filtered by stratum corneum, but after absorption by melanin, 30% of UVA hits basal cells of epidermis and still 20% reaches reticular dermis. One percent of UVA1 penetrates up to the limits of subcutis.[3] The skin penetration of visible light is even more important, but little is known about its biologic effects in human skin.

Positive and harmful effects of UVR in the skin are tightly woven as they contribute to the natural mechanisms of photoprotection. UVR that is not scattered by the superficial horny layer is absorbed by endogenous chromophores. Photochemical reactions of these absorbing biomolecules

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Sunlight, Vitamin D and Skin Cancer, edited by Jörg Reichrath.

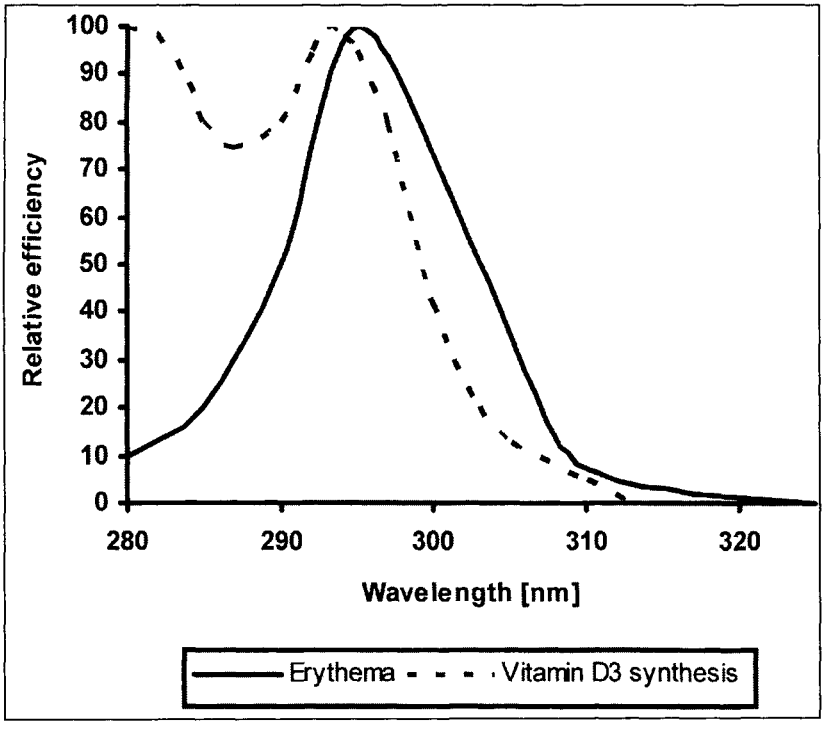

Figure 1. Action spectrum of natural terrestric UVR for solar erythema and vitamin D3 synthesis. (adapted from ref. 3).

result in alterations of skin biology that lead to the immediate or delayed UV effects represented in Figure 3.

Epidermal chromophores with absorption spectra within the UVB range are urocanic acid, melanin, aromatic amino acids such as tryptophane and tyrosine in epidermal proteins and nuclear DNA.[4] Urocanic acid is most expressed in the superficial layers of epidermis. It absorbs UVB by a trans to cis isomerization. Its synthesis from histidine liberated by filaggrin breakdown is triggered by UVBR.[3] Another major target for UVB and UVA2 are nucleotides. Absorption of UVR by pyrimidine and purine bases results in DNA photoproduct formation, mainly pyrimidine dimers, but also pyrimidine (6-4) pyrimidone photoproducts. These DNA photoproducts are continuously excised by DNA repair enzymes. If repair fails, they can lead to p53-mediated apoptosis or, after replication, to DNA mutations.[1] C→T and CC→TT mutations are considered as a nuclear fingerprint of UVB-induced photodamage. UVB-generated thymine dimers induce p53 which is a pro-apoptotic protein that helps to eliminate cells in which DNA is too heavily damaged to be repaired.[5] UVB triggers in the skin the production of cholecalciferol (vitamin D3) from 7-dehydrocholesterol (DHC). The action spectrum for this synthesis is nearly identical to the one for solar erythema (Fig. 1). UVA alone does not permit cutaneous vitamin D3 synthesis.[6] UVB exposure stimulates mitotic activity in epidermis and, to a lesser extent, also in papillary dermis that persists from days to weeks. This results in acanthosis and hyperkeratosis with an approximate two-fold thickening of these skin layers that is best characterized by the German term "*Lichtschwiele*" ("light-induced callosity"). This phenomenon provides supplementary UV protection to the underlying living cells. UVA does not induce such epidermal thickening.

While UVB effects in the skin occur by direct UVB photon absorption by the target molecules, UVA effects are mostly mediated by the formation of radicals:[1] Absorption of UVAR

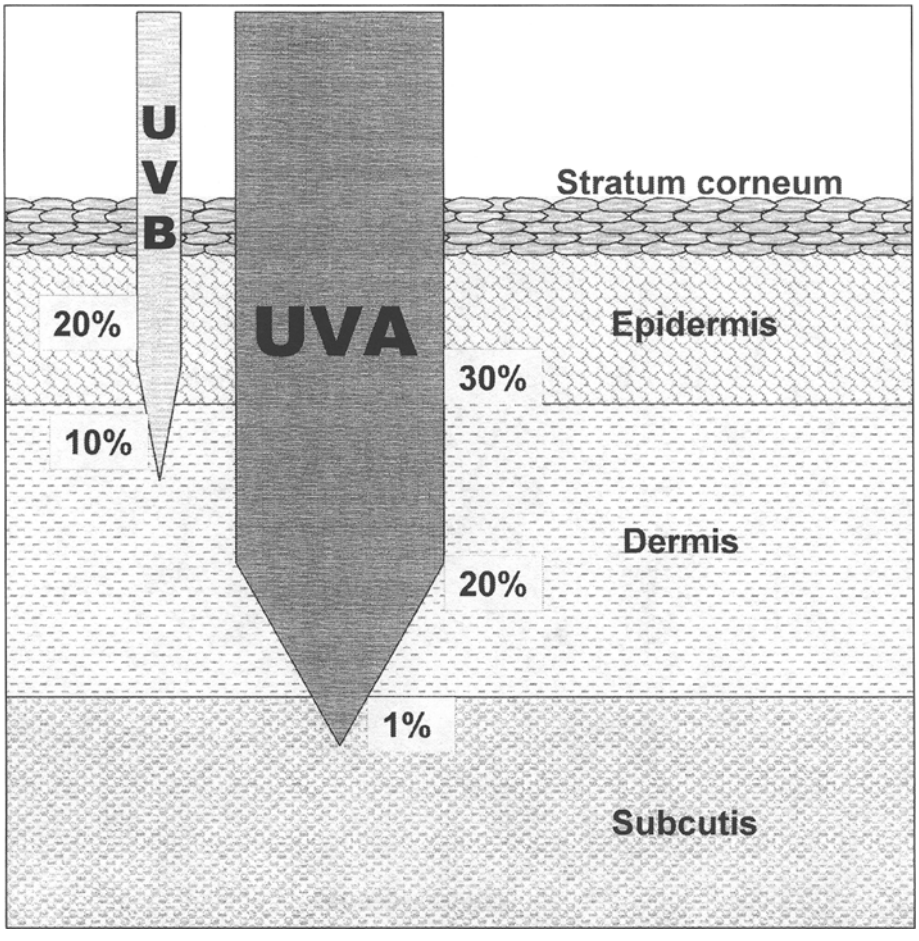

Figure 2. Penetration of ultraviolet radiation into the skin.

by appropriate chromophores such as urocanic acid, NADH, flavins and unsaturated lipids promotes these molecules into an excited state. Dissipation of this energy occurs either by internal conversion which may generate an organic radical, or, more frequently, by reaction with tissular oxygen or oxygen-containing molecules which leads to formation of so-called reactive oxygen species (ROS).[7] ROS are unstable and extremely chemically reactive molecules that can cause lipid peroxidation in plasma, nuclear and mitochondrial membranes. They can damage cellular proteins and cause DNA strand breaks and oxidation of nucleic acids.[8] The corresponding characteristic DNA fingerprint is 8-hydroxyguanine which generates G:C→ T:A mutations by error pairing of 8-hydroxyguanine with adenine instead of cytosine during following replication. These mutations generated by oxidative stress do not induce p53 and escape therefore more easily to apoptotic control than UVB-induced mutations.[9] Melanocytes seem to be more sensitive to UVA-induced DNA damage than keratinocytes.[10] Pyrimidine dimers are not only formed by direct UVBR but also by oxidative stress after UVA irradiation. DNA repair of pyrimidine dimers induced by UVAR is less effective than excision repair of UVB-induced DNA damage.[11]

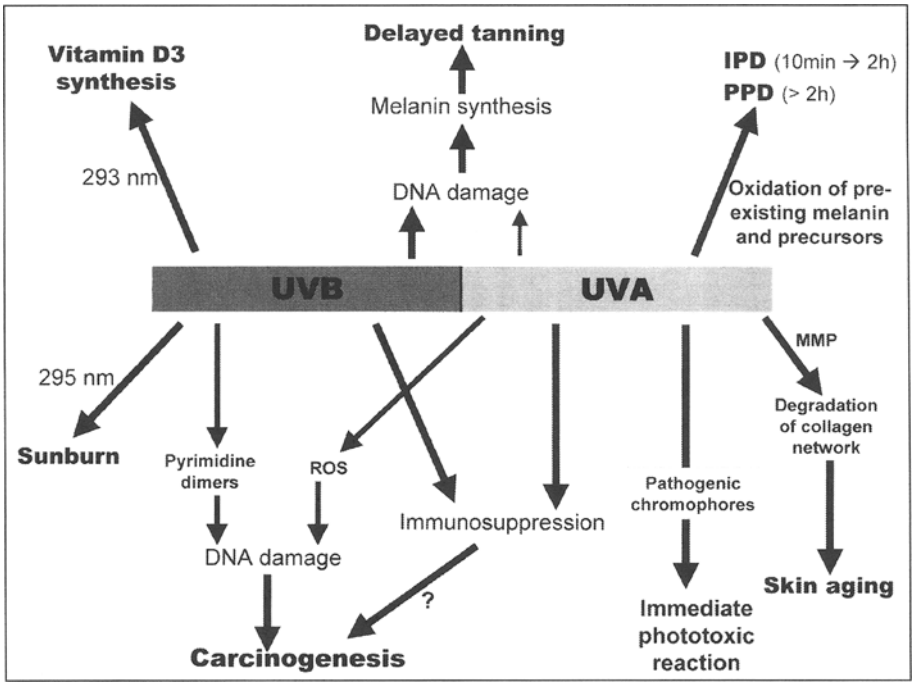

Figure 3. Biologic effects of UVR in human skin.

In response to damage to DNA and to other chromophores by UVB and UVA, cytokines and inflammatory mediators are released into the skin following UVR.[12] This is responsible for sunburn as acute clinical effect of overexposure to sunlight.

DNA damage by UVB or UVA2 triggers a tanning response in human skin.[12] Nucleotide fragments removed from the DNA after repair activate melanocyte tyrosinase, the key enzyme in melanogenesis.[13,14] UVBR seems to be most effective in stimulating de novo melanogenesis from pre-existing melanin monomers and precursors. Melanocyte dendrites elongate and branch, melanosome numbers and sizes increase and their transfer from melanocytes to keratinocytes is enhanced. This results in delayed tanning that becomes visible within 3 days after UV exposure.[12] In white skin, melanosomes are diffusely distributed within keratinocyte cytoplasm but they aggregate above the nucleus to form a kind of cap. Melanin is a large opaque molecule absorbing throughout the UV and visible light band. It is photostable, i.e., it converts the absorbed energy into heat rather than into chemical energy.[1] Both constitutive and induced melanin pigmentation protect against UV-induced DNA damage. UVA-induced tan seems to be less protective than the one induced by UVB.[15] This may be explained by the more basal localization of UVA2-induced pigmentation and the lack of epidermal thickening after UVAR. UVA2, UVA1 and short-wave visible light also induce another kind of pigment reaction after exposure: In little doses, these wavelengths generate a greyish skin color within 15 minutes after exposure that is called immediate pigment darkening (IPD).[12] It progressively declines and disappears within 2 hours. Higher UVA doses induce a longer-standing pigmentation of more brownish color called persistent pigment darkening (PPD) that persists after 2 hours. IPD and PPD do not represent de novo melanin synthesis, but they are a product of photo-oxidation of pre-existing melanin and precursors in presence of oxygen. Neither IPD nor PPD provide protection against UV-induced skin damage. They do not prevent sunburn.

Oxidative stress by UVAR can be massively enhanced by the presence of pathogenic chromophores in the skin that generate after UV irradiation far greater amounts of ROS than do cutaneous chromophores under normal conditions. The resulting acute cutaneous inflammation is addressed to as phototoxic reaction. Examples of phototoxic agents are furocoumarins contained in plants causing phytophotodermatitis after UVA irradiation or phototoxic drugs, e.g., cyclins.

Penetrating up to the dermis, UVAR is responsible for photoaging changes: The action spectrum for these degrading mechanisms lies mainly in the UVA1 band. UVB alone does not induce photoaging. UVA induces a series of matrix metalloproteinases that degrade the dermal collagen framework.[7] The presence of collagen detritus inhibits dermal procollagen synthesis and thereby aggravates the degenerative process.[16] UVA-induced oxidative stress also increases elastin messenger RNA levels in dermal fibroblasts which explains the elastotic changes that are characteristic of photoaged skin.[17]

Both UVA and UVB have immunosuppressive potential even at suberythemal doses:[18] After UV irradiation Langerhans cells in the skin are diminished in number and their morphology and function are altered. This effect is used for therapeutic purposes in dermatologic phototherapy. UVA suppresses delayed-type contact hypersensitivity.[19] Nghiem et al showed in a mouse model that even established systemic immune response is impaired by short-wave UVA.[20] It remains unclear, however, if UVA2 effectively suppresses anti-microbial immune response in humans.

The 20-fold increased risk of skin cancer in therapeutically immunosuppressed organ transplant patients suggests a role of the immune system in preventing those skin tumors. Photo-induced immunosuppression is therefore thought to contribute to the carcinogenic effect of UVR. The mutagenic action of UVR is physiologically controlled by several mechanisms: DNA repair enzymes in first line, pro-apoptotic regulation, e.g., by p53 in second line and cellular immune defense in third line. UVR can affect each one of these three defense lines: UVAR has been shown to inhibit DNA repair enzymes.[9,11] When mutations concern the p53 gene, apoptosis control is impaired and actinic keratoses, squamous and basal cell carcinomas may arise.[21] When UV-induced DNA mutations hit the patched gene, this can contribute to the carcinogenesis of basal cell carcinoma.[22] Finally the UVR-induced cutaneous immunosuppression probably concerns in the same way local anti-tumor immunity, although this has not been demonstrated in human skin so far.

Topical Photoprotection Agents

The numerous deleterious effects of UVR make protective measures necessary. Total avoidance and protective clothing are without any doubt the most effective methods but they are not practicable for daily consequent protection. Moreover, modern lifestyle going along with a great popularity of sunbathing encourages acute intermittent sun exposure. For this reason topically applied sunscreens are since 40 years the most used photoprotective means.

Suncare products are available as oils, creams, lotions, sprays, gels and sticks. They are composed of different UV filter agents and, depending on their galenic presentation, of moisturizers, conservatives and often alternative photoprotectants such as antioxidants. UV protection increases with filter concentration in sunscreens, but toxicity and poor cosmetic acceptance limit UV filter concentration for in vivo use in human beings. Classic recommendation for sunscreen use is to apply 15 to 30 minutes before sun exposure and to repeat application every two hours. The product has to be reapplied earlier after activity that may wash or rub off the sunscreen, i.e., after swimming, sweating or towel drying. "Water-resistant" suncare products are defined as protecting skin for 40 minutes of bathing whereas "waterproof" (or "very water-resistant" in the EU) sunscreens protect for 80 minutes.[23] The term "remanence" describes a sunscreen's resistance to external elimination by water, sweat or rubbing. Tightly related to remanence is a product's "substantivity" that characterizes the capacity of a filter substance to fix to structures in the upper epidermis which ensures a long lasting action.

The ideal sun protection agent should provide high protection that is equally effective against UVA and UVB. Moreover, it should be waterproof, sweat-proof, photostable, cosmetically acceptable and nontoxic.

Regulations and Marketing

Sunscreen marketing is submitted to national legislation. These regulations are harmonized among the member states of the European Union where UV filters are listed as cosmetics by the European Cosmetic Toiletry and Perfumery Association (COLIPA). In the United States, in contrast, sunscreens are considered as over-the-counter drugs that are subject to Food and Drug Administration (FDA) regulation. They must therefore undergo considerable safety and allergy testing in clinical trials that is responsible for high costs to the manufacturers and important delay before marketing as compared to the EU where new filter products can enter the market more rapidly. Strict FDA regulations—and bureaucracy—have conducted to a kind of regrettable underdevelopment of the US suncare market. For this reason, although it was in the United States where the first commercial UV filter preparation was available in the 1920s, 80 years later French, German and Swiss manufacturers are global market leaders in this domain.

The following discussion of filter substances that are listed in Table 1 is adapted to the positive list of the European Cosmetics Directive. I regard this filter selection as more representative of today's possibilities in the UV filter domain than the substances listed in the US FDA sunscreen monograph. The UV filters in the European list are commercially available in most countries outside the US.

Measuring Photoprotection

The sun protection factor (SPF) of sunscreens expresses their capacity of protection from erythema after UV exposure. SPF therefore essentially translates protection from UVBR.

For SPF testing, erythema is induced by a xenon lamp solar simulator. The smallest dose causing a minimally perceptible erythema with well-defined borders at 24 hours after one single irradiation is called minimal erythema dose (MED). Basic MED mainly depends on the individual's natural photoprotective potential provided by constitutive and adaptive pigmentation and skin thickening, but also on variable parameters such as nutrition and drug intake. The standard product dose for SPF testing is 2 mg of finalized sunscreen per cm^2 of skin. SPF is a ratio calculated from the following formula:

$$\text{SPF} = \frac{\text{MED with the tested sunscreen}}{\text{MED without sunscreen}}$$

This MED-related procedure has the advantage compared to in vitro spectrophotometry to be directly related to the biologic consequences of UV exposure in a given individual. It is based on the individual sensitivity to UVR at a given moment. However, DNA damage and immunosuppression occur even below the erythema threshold dose. These harmful effects are not considered by SPF calculation.[24] At least theoretically, SPF permits to estimate the factor by which sun exposure can be extended in daily practice until erythema threshold: If the recommended dose of 2 mg/cm^2 is applied (which is in general not the case!) and no external elimination occurs, a SPF10 suncare product permits to stay ten times longer in the sunlight without erythematous reaction than without this protection.

The relation between the percentage of filtered UVB/UVA2 radiation and SPF is a logarithmic and not a linear one (Fig. 4). In recent years cosmetic industry gave a race to higher and higher SPFs and great SPF numbers have become for the consumer the first criterion of choice between different sunscreen products. Indeed UV absorption increases from 0% to 90% between a moisturizer without SPF and a SPF10 sunscreen, but only from 97% to 99% between a SPF30 and a SPF100 product. It has never been demonstrated that SPFs of more than 30 have any clinically relevant impact on the deleterious action of UV exposure in the skin compared to SPF30 sunscreens (which yet absorb almost 97% of erythemogenic UVR). To limit the implicit deception of the consumer by high SPF numbers which can lead to a false hope of "complete" protection and subsequent overexposure to harmful photodamage, several countries have regulated sunscreen labeling: In the European Union sunscreens with SPF of more than 50 have to be labeled "SPF50+". In Australia the SPF scale is limited to 30.

Table 1. Organic and inorganic UV filters marketed in the European Union (positive list of UV filters according to the European Cosmetics Directive, Annex VII)

INCI Name	Abbreviation	IUPAC Name	Max. Auth. Conc.	Trade Name(s)	Abs. Max.	Comments
Pure UVB filters						
PABA	PABA	4-Aminobenzoic acid	5%	PABA®	283 nm	Binding to proteins of the stratum corneum ensures good substantivity and good remanence. Photoallergic potential
Octyl Dimethyl PABA = Padimate O	OD-PABA	2-Ethylhexyl p-dimethylamino-benzoate	8%	Eusolex 6007® Escalol 507®	311 nm	
PEG-25-PABA	PEG-25-PABA	Polyethylene glycol 25 aminobenzoate	10%	Uvinul P25® Unipabol U17®	310 nm	
Octyl Methoxycinnamate = Octinoxate	OMC	2-Ethylhexyl-3-(4-methoxyphenyl) prop-2-enoate	10%	Escalol 557® Eusolex 2292® Neo Heliopan AV® Parsol MCX®	311 nm	Used in combination with other filters as not photostable in pure preparations
Isoamyl p-methoxycinnamate = Cinoxate	IMC	3-Methylbutyl 3-(4-methoxyphenyl) prop-2-enoate	10%	Neo Heliopan E1000® Uvinul N-539®	289 nm	
Camphor Benzalkonium Methosulfate	---		6%	Mexoryl SK®	295 nm	Good photostability, also permit to stabilize other UV filters such as cinnamates
3-Benzylidene Camphor	BC		2%	Mexoryl SD-20® Unisol-S-22®	295 nm	
4-Methylbenzylidene Camphor = (USAN) Enzacamene	MBC	3-(4'-Sulfo)-benzylidene- bornan-2-on	4%	Eusolex 6300® Neo Heliopan MBC® Parsol 500®	305 nm	
Polyacryl-Amidomethyl Benzylidene Camphor	---	N-[2(and 4)-(2-oxoborn-	6%	Mexoryl SW®	295 nm	

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Table 1. Continued

INCI Name	Abbreviation	IUPAC Name	Max. Auth. Conc.	Trade Name(s)	Abs. Max.	Comments
Homosalate	HMS	3, 3, 5-Trimethyl-cyclohexyl-salicylate	10%	Eusolex HMS® Neo Heliopan®	306 nm	Can reduce photodegradation of oxybenzone and avobenzone
Octylsalicylate	OS	2-Ethylhexylsalicylate	5%	Escalol 587® Neo Heliopan OS®	307 nm	
Phenylbenzimidazole Sulfonic Acid	PBSA	2-Phenylbenzimid-azol-5-sulfonic acid	8%	Eusolex 232® Neo Heliopan Hydro® Parsol HS®	308 nm	Hydrophilic filter, can improve photostability of other filters
Dimethicodiethylbenzal-malonate = Polysilicone-15	---	Benzylidene malonate polysiloxane	10%	Parsol SLX®	311 nm	Photostable, used to stabilize BMDBM
Octyl Triazone	OT	2,4,6-tris[p-(ethylhexyl-oxycarbonyl)anilino]-1,3,5-triazine	5%	Uvinul T15®	314 nm	
Octocrylene	OC	2-Ethylhexyl-2-cyano-3, 3-diphenylacrylate	10%	Eusolex OCR® Neo Heliopan 303® Uvinul N-539®	303 nm	Photostable filter, used to stabilize cinnamates
Benzophenone UVB-UVA2 broad spectrum filters						
Benzophenone-3 = Oxybenzone	BENZ-3	2-Hydroxy-4-meth-oxy-benzophenone	10%	Escalol 567® Eusolex 4360® Neo Heliopan BB® UVAsorb MET/C® Uvinul M40®	288 and 325 nm	Photolabile, important photoallergic potential; warning "contains oxybenzone" to be printed
Benzophenone-4 = Sulisobenzone	BENZ-4	2-Hydroxy-4-methoxy-benzophenone-5-sulfonic acid	5%	Escalol 577® UVAsorb S5® Uvinul MS40®	288 and 366 nm	Good photostability, photoallergic cross-reaction with oxybenzone

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Table 1. Continued

INCI Name	Abbreviation	IUPAC Name	Max. Auth. Conc.	Trade Name(s)	Abs. Max.	Comments
Pure UVA filters						
Butyl Methoxy-Dibenzoylmethane = Avobenzone	BMDBM	1-(4-tert.	5%	Eusolex 9020® Parsol 1789®	356 nm	Poor photostability in its pure form, needs to be stabilized by association with other filters such as BC, OC or Polysilicone-15
Dioctyl Butamido Triazone	DBT	4,4'-[(6-[4-((1,1-Dimethylethyl)-amino-carbonyl)-phenyl-amino]-1, 3, 5-triazine-2, 4-yl)-diimino]-bis-(benzoic acid-2-ethylhexylester)	10%	UVAsorb HEB®	345 nm	
Disodium Phenyl Dibenzimidazole Tetrasulfonate	DPDT	2,2'-(1,	10%	Neo Heliopan AP®	345 nm	hydrosoluble
Diethylamino Hydroxy-benzoyl Hexyl Benzoate	DHHB		10%	Uvinul A Plus®	330 and 370 nm	photostable
Last generation UVB-UVA2-UVA1 broad spectrum filters						
Terephthalidene Dicamphor Sulfonic acid = (USAN) Ecamsule	MSX	3,3'-(1,4-Phenylene-di-methylidene)bis-(7,7-dimethyl-2-oxobicyclo-(2.- 2.1)heptane-1-methanesulfonic acid	10%	Mexoryl SX®	345 nm	Hydrosoluble, photostable

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Table 1. Continued

INCI Name	Abbreviation	IUPAC Name	Max. Auth. Conc.	Trade Name(s)	Abs. Max.	Comments
Drometrizole Trisiloxane = Silatrizol	MXL	2-(2H-benzotri-azol-2-yl)-4-meth-yl-6-(2-methyl3-(1,-,3,3-tetramethy-l-1-(trimethyl-	10%	Mexoryl XL®	303 and 344 nm	Liposoluble, photostable
Methylene bis-Benzo-triazolyl Tetramethyl-butylphenol = (USAN) Bisoctrizole	MBBT	2,2'-Methy-lene-bis-6-(2H-benzo-triazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)-phe-nol	10%	Tinosorb M®	306 and 360 nm	Very photostable, UV absorption and reflection, hydrosoluble
Bis-Ethylhexyloxyphenol Methoxyphenyltriazine = Anisotriazine = (USAN) Bemotrizinol	BEMT		10%	Tinosorb S®	305 and 345 nm	Excellent photostability, oil soluble, water resistant
Inorganic filters						
Titanium Dioxide (micronized)	TiO_2		25%		Depending on particle size: UVB-UVA-visible light	Excellent UVB and UVA2 coverage, less in UVA1
Zinc Oxide (micronized)	ZnO		25%			Good UVA1 coverage, less effective in UVB

Abbreviations: INCI = International Nomenclature of Cosmetic Ingredients; IUPAC = International Union of Pure and Applied Chemistry; Max. auth. conc. = Maximum filter concentration authorized by the European Cosmetics Directive for finalized sunscreen products; Abs. Max. = Wavelength at which maximum absorption occurs with the filter; USAN = United States adopted name.

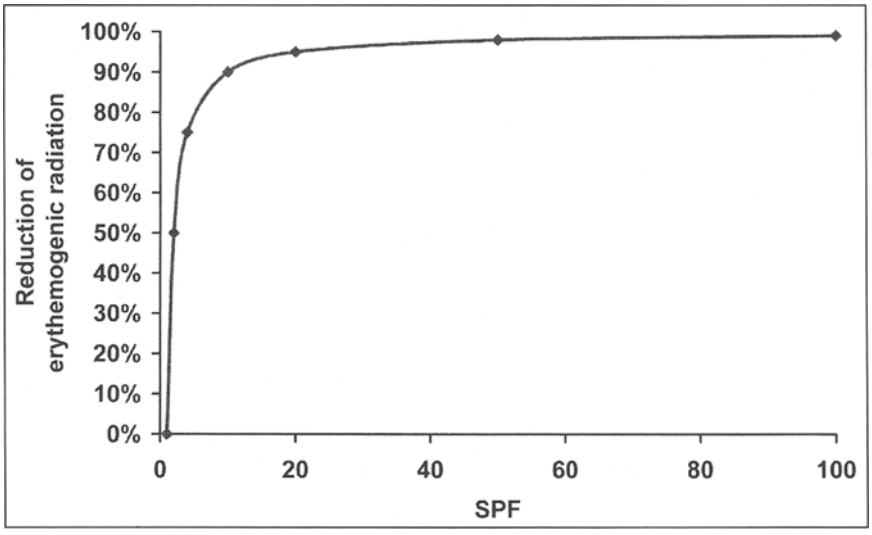

Figure 4. Reduction of erythemogenic UVR by sunscreens.

UVA protection is more difficult to quantify than UVB-SPF, because UVA is few erythemogenic. Currently there is no uniformly accepted standard method for measuring UVA protection by sunscreens. The most commonly used methods are in vivo PPD and critical wavelength assessed in vitro by spectrophotometry. Critical wavelength is defined as the wavelength below which 90% of the sunscreen's UV absorbency occurs as measured in the band region from 290 to 400 nm.[25]

Organic UV Filters

Organic UV filter substances mainly act by absorption of photons in the UV wavelength band. They are aromatic molecules conjugated with carbonyl groups. These chromophores absorb UV photons through electron resonance delocalization in the aromatic compounds that raise the molecule from the electronic ground singlet state S_0 into an excited electronic state S_1 or higher. In most classic UVB absorbers such as PABA this leads to a transitory polarization of the organic molecule (Fig. 5). Organic UV filter molecules capture photons of a more or less specific wavelength λ around their absorption maximum. No organic UV filter, especially not the "classic molecules", cover the entire UV spectrum. For this reason, finalized sunscreen products are in general an association of several filter substances. The absorbed energy is dissipated by vibronic relaxation that delivers heat via collisions with the surrounding medium.[26] A minor part of energy may also be emitted in form of fluorescent radiation (λ = 400-700 nm), i.e., visible light, with wavelengths that are longer than those of the initial photon. Although this kind of radiation is harmless, it has to be limited for the cosmetic acceptance of the UV filter. Energy release permits the excited filter molecule to return to its ground state where it is again available to absorb additional photons. Filters that perfectly repeat this cyclical process without undergoing significant chemical change are classified as photostable. Photostable filters can retain their UV-absorbing potency during long exposures.

The excited form of filter molecules after UV absorption has to be very short-lived in order to prevent chemical reactions between the filter and tissular proteins or oxygen which could lead to photoallergic or phototoxic reaction. Unfortunately such reactions, mainly photoallergy, have been described repeatedly with PABA derivatives, cinnamates and benzophenones.[27,28] Several molecules have been withdrawn. The photosensitization to benzophenone-3 (oxybenzone) is particularly severe, because photoallergic cross-reactions are known with benzophenone-4 (another broad

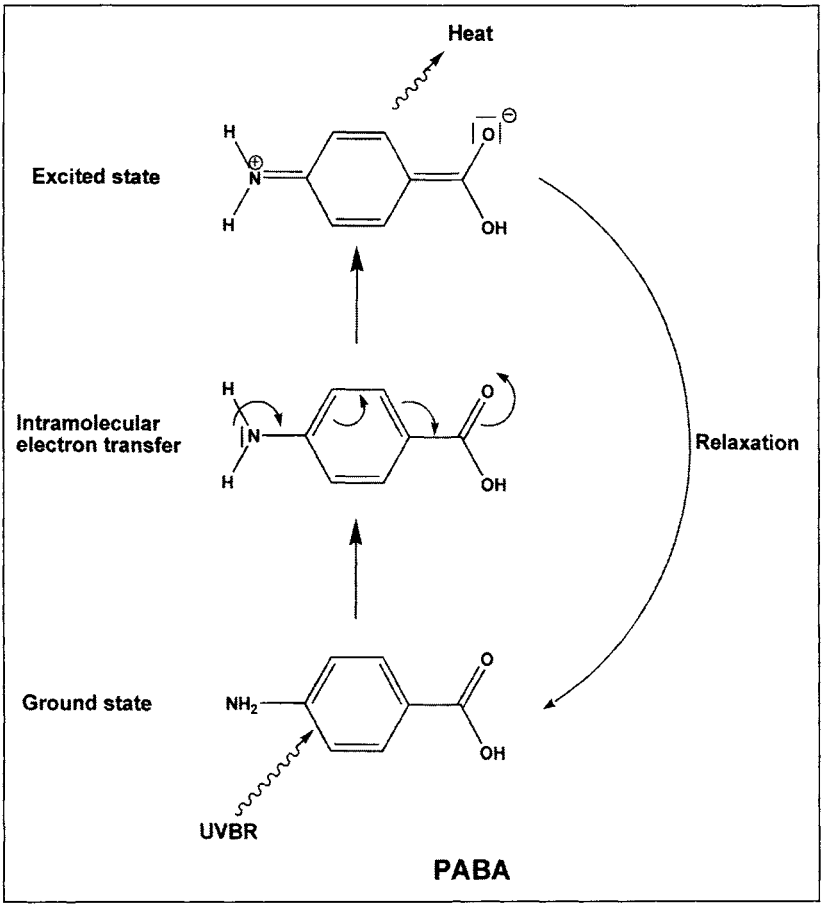

Figure 5. Mechanism of UVB absorption by the "classic" UV filter PABA.

spectrum filter), topically applied ketoprofen and even with systemically administered fenofibrate.[27] Considering the large use of sunscreens, however, these photocontact allergies to UV filters remain relatively rare events. In the case of eczema in sun-exposed skin areas that have been treated with sunscreens, not UV-related contact sensitization to UV filters as well as contact and photocontact allergy to other components of sunscreens besides the filters have to be eliminated.

Some UVB filters such as cinnamates undergo after UV absorption an intramolecular trans to cis isomerization. Others experience definitive structural transformation which alters their protective capacity. This is a major problem with the currently used UVA filter avobenzone which looses considerably of its photoprotective potential after irradiation in its pure form.[29] As photoprotection by sunscreens is tested by single irradiation, the photounstable character of the concerned molecules is not assessed by standard test protocols. Photounstable filters can be stabilized by association with other organic UV filters (see Table 1) or with inorganic filters. In the US an association of avobenzone and oxybenzone with 2-6-diethylhexyl naphtalate, a photostabilizing solvent, has recently been marketed in order to overcome the avobenzone photodegradation problem and to comply with FDA regulations (Helioplex®, Neutrogena). But this combination still suffers from the presence of oxybenzone as a photoallergenic filter with significant systemic absorption.

Indeed classic organic UV filters are little-sized more or less lipophilic molecules. These chemical properties allow easy penetration at least into the deeper layers of the epidermis where

the filters encounter living cells (Fig. 6) which explains the incidence of photoallergy as a clinical manifestation of immunologic reaction to filter molecules having formed haptens after photoactivation. Percutaneous systemic absorption of organic UV filters has been reported for several filter molecules: Sarveiya et al found 1% of topically applied oxybenzone in the urine of 48 hours after sunscreen use.[30] Janjua et al detected oxybenzone, octyl-methoxycinnamate (OMC) and 4-methylbenzylidene camphor (MBC), i.e., representative molecules of 3 different families of organic UVB filters, in plasma and urine of healthy volunteers.[31] The penetration of systemically absorbed sunscreens into the organs and their clearance have never been assessed. One study reported an estrogen-like activity of octyl dimethyl PABA (OD-PABA), OMC, homosalate, 4-methylbenzylidene camphor, oxybenzone and avobenzone in vitro in MCF-7 breast cancer cells and in vivo in the immature rat uterotrophic assay.[32] These results were not confirmed in human adults.[31] Sunscreen absorption and endocrine activity have never been examined in prepubertal children who are not only more prone to systemic absorption than adults but are also more sensitive to low levels of hormone action due to their low levels of endogenous reproductive hormones.

For these penetration problems, the use of organic UV filters is not recommended for young children who have an immature stratum corneum and for patients with pre-existing skin lesions that may go along with an impairment of the epidermal barrier function. In these two groups of users, penetration of organic filters is probably yet more important than for the general skin-healthy adult population. They may be exposed to a higher risk of photocontact sensitization to organic filter molecules and to systemic absorption of larger amounts of these substances.

Besides their proper dermal penetration, organic UV filters have been shown to enhance topical penetration of herbicides and insecticides. This has been demonstrated for the herbicides 2,4-dichlorophenoxyacetic acid and paraquat and for the insecticides parathion and malathion.[33] The filters OD-PABA, OMC, homosalate, octyl salicylate, octocrylene, oxybenzone and benzophenone-4 (molecules from 5 different chemical subgroups of organic UVB filters) were tested in a mouse model and in human split skin in vitro:[34] All but octocylene were found to increase cutaneous

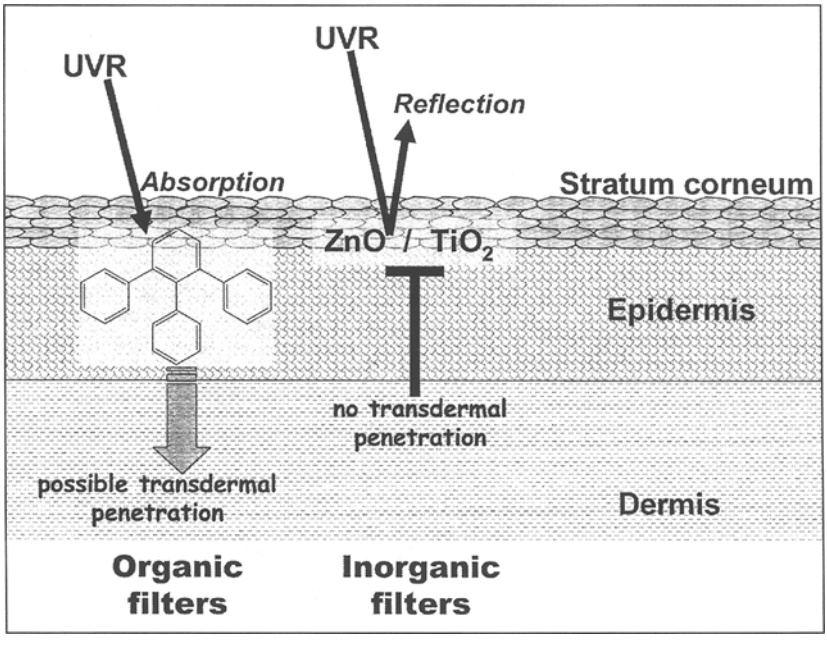

Figure 6. Organic and inorganic UV filters on the skin: mechanism of UV protection and penetration of the filters into the skin.

penetration of the applied herbicides and insecticides. This finding is particularly alarming for agricultural workers using pesticides who are encouraged to wear sunscreens for their outdoor work and for fair-skinned individuals from the temperate zone who seek to protect themselves during a stay in tropical countries from both intense sunlight and insect attack.

By reaction with tissular proteins, DNA or oxygen, photounstable UV filters may cause harmful or even procarcinogenic effects in the skin: In vitro studies found DNA nucleotide dimer formation to be enhanced under PABA treatment,[35] UVR-induced mutagenity to be increased by isoamyl p-methoxycinnamate and tissular radicals to be formed by photo-degraded avobenzone. However, the in vivo significance of these findings is doubtful and a review of available clinical data concluded that UV filters, at least when used occasionally, do not pose a human health concern.[36]

The first sunscreen in the world appeared in 1928 in the United States with the commercial introduction of an emulsion that contained the two organic UVB filters benzyl salicylate and benzyl cinnamate.[1] PABA was patented in 1943. The main concern when the first topical sunscreens were developed was to provide protection from UVB-induced sunburn. During the following decades new chemical filter families with more and more derivatives were developed and optimization of their concentration and combination of several filters with complementary absorption peaks allowed higher SPFs. Up to the 1980s, high SPFs in a cosmetically pleasant galenic presentation were sufficient to satisfy sunscreen users worldwide. Absence of UVA protection was tolerated as it provided desirable tan without risk of sunburn. With increasing evidence about the role of UVAR in the long-term deleterious effects of sun exposure, organic filters with absorption maximum in the UVA band range and benzophenones being the first UVB/UVA2 broad spectrum filters were marketed. But benzophenones provide only insufficient protection in the long-wave UVA1 band region. Because of photolability and dermal penetration of classic organic filters, the above described adverse events—mostly photoallergy and contact dermatitis—were successively reported. Research therefore focused on the development of filter substances providing both a maximum of product safety and an absorbing coverage of the entire UV spectrum, but permitting on the other hand an association with classic UV filters in finalized products.

In 1993 L'Oréal (Clichy, France) introduced the first representative of a new generation of organic broad spectrum UV filters: terephthalidene dicamphor sulfonic acid (Mexoryl® SX, MSX). MSX is a water-soluble filter that is suitable for day wear sunscreen formulations including sunscreen-containing moisturizers and facial formulations. In 1998 the same manufacturer completed its range of products by an oil-soluble substance: drometrizole trisiloxane (Mexoryl® XL, MXL), a hydroxybenzotriazole derivative. This molecule is composed of two different chemical subunits: The 2-hydroxyphenyl benzotriazole subunit contains the UV-absorbing potential over the whole UVB, UVA2 and UVA1 wavelength spectrum with two different absorption peaks, one in the UVB band ($\lambda = 303$ nm) and another one at the limit between UVA2 and UVA1 ($\lambda = 344$ nm). The siloxane subunit of MXL confers to the molecule a lipophilic character that renders it suitable for water-resistant sunscreen formulations, including those worn on the beach and during vigorous physical exercise.[1] Another hydroxybenzotriazole derivative was commercialized in 1999 by Ciba Specialty Chemicals (Basel, Switzerland): The hydrosoluble methylene bis-benzotriazolyl tetramethylbutylphenol (MBBT, Tinosorb® M) covers, with two absorption peaks, the entire UVB and UVA spectrum. This organic filter has the particularity to associate for its UV-protective action both absorbing and reflecting properties. UV reflection is normally only seen with inorganic UV filters. MBBT consists of microfine organic particles that are dispersed in the aqueous phase of sunscreen emulsions.

The latest oil-soluble UV filter is bis-ethylhexyloxyphenol methoxyphenyltriazine (BEMT, Tinosorb® S). It was introduced in 2002. The mechanism of action of BEMT is illustrated in Figure 7: BEMT is a large polyaromatic molecule. Its size impedes dermal penetration in spite of its lipophilic property. The asymmetric structure of the molecule harbors separate absorption sites for UVBR and UVAR. After absorption of UV photons the molecule is promoted into an excited state that undergoes photo-tautomerism with intramolecular proton transfer. The duration of this isomerization is in the order of 10^{-12} second. This extremely short time

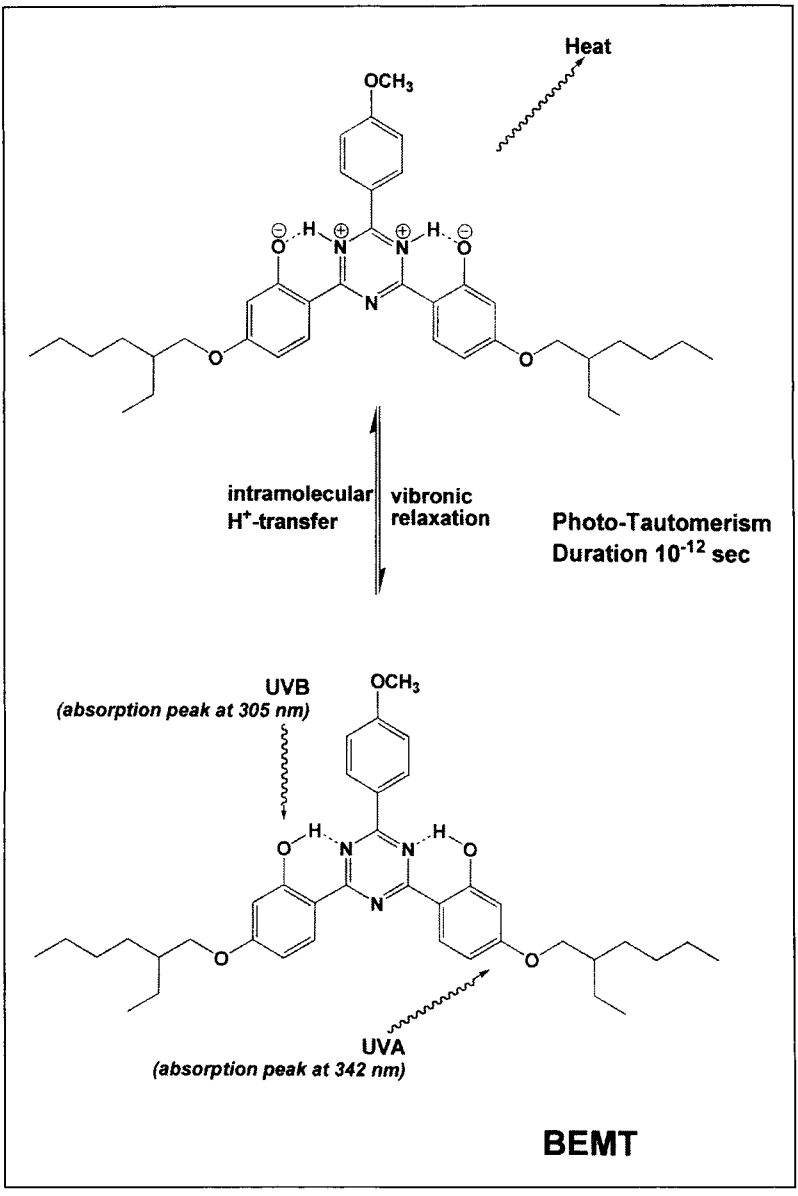

Figure 7. Mechanism of UVA and UVB absorption by bis-ethylhexyloxyphenol methoxy-phenyltriazine (BEMT, Tinosorb® S)[26].

span does not permit any external chemical reaction to be triggered. This prevents the formation of radicals or haptens from the photoexcited BEMT molecule. BEMT returns by vibronic relaxation with heat release into its energetic ground state in chemically unchanged form and is again ready to absorb UVR.[26]

Mexoryls and tinosorbs provide strong absorbency up to the UVA1 range and excellent photostability. Their use in commercial sunscreen preparations permits to achieve significantly better UVA protection as measured by the PPD protocol. In order to obtain high UVB-SPF and

UVA-PF which cannot be achieved with one filter alone, they are nevertheless associated with classic organic filters and inorganic pigments in commercialized sunscreens. They can stabilize photolabile filters such as cinnamates or avobenzone.[37] Percutaneous absorption, photoallergic and phototoxic reactions have not been reported so far with these last generation organic filters. Both MBBT and BEMT do not have estrogenic or androgenic activity in vitro.[38]

Thirteen years after its marketing in most parts of the world, MSX finally obtained FDA approval in July 2006. Tinosorbs are still not available in the United States.

Inorganic UV Filters

Inorganic UV filter substances are chemically inert pigments that stay in the upper layers of the epidermis and stratum corneum. They reflect or scatter radiation (Fig. 6). The degree of reflection and scattering by these pigments is strongly dependent on their particle size and shape. Two inorganic oxides are used for UV protection in humans: zinc oxide (ZnO) and titanium dioxide (TiO_2). In their nonmicronized form, with a particle size of 200 to 500 nm, inorganic filters act as opaque radiation blockers that reflect not only UVR in both the UVB and the UVA spectrum, but also visible light and infrared radiation. In this form they are particularly suitable for protection in visible light-induced photosensitivity diseases such as porphyrias.[39] However, the reflection of visible light makes inorganic sunscreens visible to the eyes and thus cosmetically less acceptable. Iron oxide, a reddish pigment with absorbing capacity in the UVA range, is sometimes added to large sized particle inorganic filter preparations to correct their "white" look. Cosmetic acceptability of inorganic UV filters is improved by micronization of the particle size to 10-50 nm. Decreasing the particle size reduces reflection, mainly of longer wavelengths and shifts protection towards shorter wavelengths by increasing absorbency by micronized filter particles.[1] Microfine ZnO protects over a wide range of UVA, including UVA1, but is less effective against UVBR. It is very photostable and does not react with organic UV filters.[40] Micronized TiO_2 provides good protection in the UVB and UVA2 range, but is insufficient for UVA1. ZnO and TiO_2 are therefore perfectly complementary in one sunscreen preparation. They are frequently associated to organic UV filters for their photostabilizing properties. Although the particle size of micronized TiO_2 is smaller than the one of ZnO, it has a higher reflective index and appears therefore whiter than ZnO.[1,40] Micronized TiO_2 is also more photoreactive than ZnO by UV absorption: The crystalline forms of TiO_2 are semiconductors. UVB or UVA2 photons can promote electrons from the valence band to the conduction band, generating simple electrons and positively charged spaces called holes. After formation, electrons and holes either recombine or migrate rapidly in about 10^{-11} second to the particle surface where they react with the surrounding medium. In aqueous environment, this can lead to formation of ROS and in vitro cellular DNA damage has been reported in one study.[41] As inorganic filters do not penetrate into layers of epidermis containing living cells, this phenomenon does not seem to play a significant role in clinical use of sunscreens. Nevertheless, the photoreactivity of inorganic UV filters reduce their protective efficacy.

For this reason, TiO_2 and ZnO particles are often coated with dimethicone or silica which stabilizes the filter substances.[1] Another possibility is to integrate micronized inorganic UV filters together with organic filters into solid lipid nanoparticles (SLN). In SLN, the inorganic filter pigment is embedded in association with lipophilic organic UV filters such as cinnamates into a drug-carrying solid lipid phase at nanoscale that is coated with triglycerids (Fig. 8). This triglycerid envelope permits to establish two-phase UV filter delivery systems by dispersion of SLN within an aqueous phase by high-pressure homogenization.[42,43] In SLN, organic UV filters and TiO_2 stabilize each other and their association yields higher SPF than the two filters separately. The embedding into a solid lipid matrix inhibits the direct contact between TiO_2 crystals and water and thereby prevents the formation of ROS by TiO_2 photoreactions. It furthermore reduces the intrinsic irritation provoked by TiO_2 and the photoallergenic potential of cinnamate filter molecules.[43]

Inorganic UV filters are characterized by good substantivity by fixation to stratum corneum proteins and little or no penetration into the skin. ZnO in a phenyl trimethicone solution was even shown to inhibit transdermal pesticide penetration, whereas TiO_2 alone had no effect.[33]

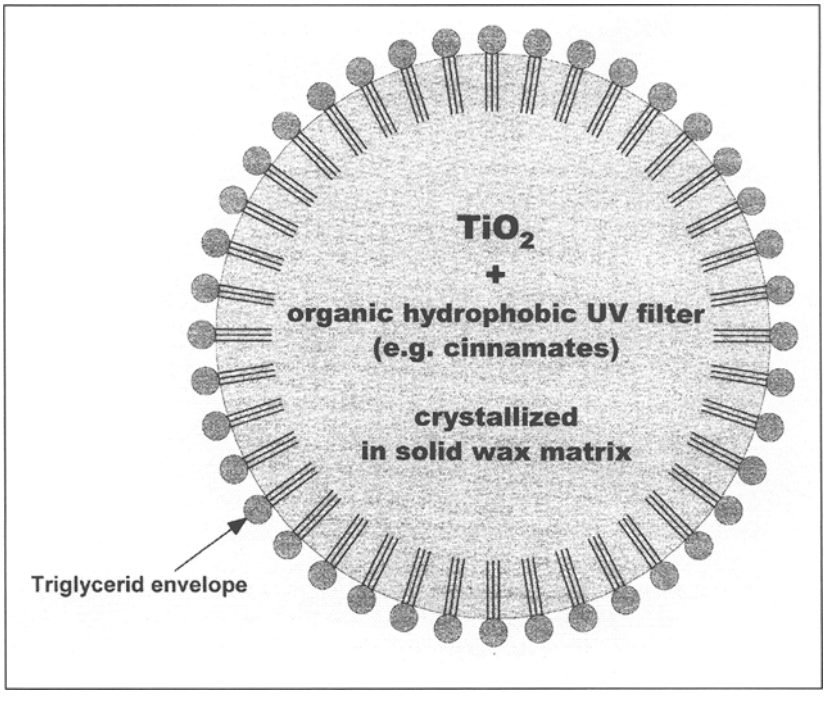

Figure 8. Solid lipid nanoparticles (SLN) for coating of inorganic UV filters.

Immunologic sensitization to inorganic filter pigments has not been reported so far.[1] They are therefore ideal sunscreen agents for young children and patients with pre-existing skin lesions.

Efficacy of Sunscreens

Sunscreen SPF is defined by the product's capacity of protecting from UV-induced erythema. If applied correctly, sunscreens are therefore by definition effective against sunburn.

But today, consumers expect sunscreen use to also protect them from the other harmful effects of UVR that have been developed above. It is difficult to comment on the "real" efficacy of sunscreens for other indications, especially for tumor prevention, for two major reasons:

- Studies on the protective efficacy of sunscreens against skin aging and cutaneous carcinogenesis often use animal models in which these changes are induced within weeks after UV irradiation. However, in human beings, cutaneous carcinogenesis is a multi-step process developing over several decades. As skin tumor formation in humans seems to be a much more complex scenario than in mouse models, the observations obtained in these models can be transferred to the situation in humans only with great caution. In the same way, murine skin aging models do not necessarily reflect the conditions in human skin.
- Skin tumors arising a very long time after irradiation, up to 40 years, the entire epidemiologic data available today was obtained with sunscreen agents commercialized before the introduction of UVA1/UVA2 filters and last generation broad band filters. Although sunscreen use was already wide-spread in the 1980s, the advances in sunscreen development achieved since that time concerning the coverage of the entire UVA spectrum and filter photostability do without any doubt contribute to the long-term efficacy of sunscreens.

Factors affecting the efficacy of sunscreens are essentially inadequate application and external elimination.

Whereas SPF testing protocol is based on an application of 2 mg/cm^2 of sunscreen, under real life conditions users were found to apply rather amounts about 0.5 mg/cm^2. Under these application conditions, a SPF50 sunscreen indeed provides a SPF of only 5.[44] Indeed protection increases exponentially with increasing sunscreen concentration.[45] Some sites such as back, lateral sides of the neck and ears are regularly missed during sunscreen application. Because of their white appearance, inorganic sunscreens are often applied in lesser amounts than organic filters which obviously even more decreases their efficacy compared to the one that could be expected from their UVB-SPF/UVA-PF.[46]

Most people apply sunscreens only occasionally for important and planned sun exposure, mostly during leisure time and holidays. However, as the greatest part of cumulative lifetime UV exposure occurs outside these periods, i.e., through short-time but repeated daily outdoor stays and by UVAR indoor, it is not surprising that daily use of a sunscreen is more protective against UV-induced skin changes than intermittent use of the same product.[47]

When correctly used, sunscreens provide a satisfactory but not complete protection against photodermatoses: Light forms of polymorphous light eruption, actinic herpes labialis, solar urticaria and actinic reticuloid can be prevented by broad spectrum sunscreens.[1,48] Broad-spectrum sunscreens with high UVB-SPF also protect lupus erythematodes patients from flares.[49]

UVAR is the principal responsible for UV-induced skin aging.[50] For this reason, only studies that assess dermal changes after solar simulating irradiation, i.e., containing UVA, are representative of the skin aging process in humans. In reconstructed epidermis,[51] mouse models,[52,53] and humans in vivo,[54] only sunscreens with high protection factors in both the UVB and the UVA spectrum were found to diminish skin aging effects. But even with MXS the protection remained incomplete although the test was performed with little UVA doses and after repeated long-term exposure, elastotic changes appeared even in sunscreen-protected skin areas. Phillips et al emphasized the importance of consequent daily application in prevention of skin aging: They showed that forgetting sunscreen application only every fourth day significantly impairs treatment benefits in long-term use.[47] But the efficacy and safety of sunscreens in skin aging prevention has not been established for long-term use over several years.

To prevent cutaneous photo-immunosuppression, sunscreens must provide protection against both UVBR and UVAR. But even broad spectrum sunscreens can only partially restore Langerhans cell numbers, delayed-type hypersensitivity to recall antigens and contact hypersensitivity (CHS) response to chemical allergens.[24,51,55] A nearly complete conservation of CHS is only obtained with sunscreens offering high UVA-PPD protection with a superiority of mexoryls compared to avobenzone.[51] In humans, sunscreen protection against photoinduced immunosuppression is not correlated to SPF and it is inferior to protection from erythema.[24]

The protective value of sunscreens against photocarcinogenesis is difficult to access because of the long time span between the beginning of UV exposure and the appearance of a clinically perceptible skin tumor in humans. Although sunscreens are widely used since the 1960s, the incidence of melanoma and nonmelanoma skin cancer is steadily increasing. This raises some doubt about the capacity of sunscreens to prevent cutaneous photocarcinogenesis. Two randomized case-control studies, one conducted over only six months[56] and another one conducted over 4.5 years,[57] found a reduced number of new actinic keratoses (AK) and a higher number of remission of pre-existing AK in the group treated with daily sunscreen compared to the placebo group. The benefit of daily sunscreen application was in the order of an average of one AK avoided per person over the 4.5-year study period.[57] Concerning squamous cell carcinoma (SCC), Wulf et al found a delay in the incidence of UV-provoked tumors in a mouse model with sunscreen protection compared to an unprotected control group. But finally, earlier or later even in the sunscreen-protected group nearly all mice developed skin cancer.[58] Although sunscreens seem to have some delaying effect on AK and SCC, a complete protection cannot be achieved even by daily application. But none of these studies examined last generation broad spectrum filters. For the evaluation of this new substance group, only preclinical assays are available to date:

Several studies in mice[59] and in humans[51,60,61] have shown an inhibition by sunscreens of p53 expression increase after UV irradiation, considered as a marker of DNA damage, but no impact on the appearance of p53 mutations. In these studies, TiO_2 was superior to OMC. A product containing MSX, MXL, avobenzone and TiO_2 with an UVA-PF (PPD) of 14 completely suppressed p53 expression in humans whereas another sunscreen having a UVA-PF of 7 and containing only avobenzone and TiO_2 as UVA filters did not.[51] The use of reduced p53 expression as efficacy marker of sunscreens is subject of controversy: Indeed p53 is a pro-apoptotic protein that intervenes in the organism's natural anti-tumor defense. Its suppression is therefore not an ideal criterion for the evaluation of anti-photocarcinogenic activity.

MSX and OMC were found to provide equal protection against pyrimidine dimer formation in mice that were irradiated with a solar simulator. But when polychromatic light was used that contained only UVA and visible light, MSX protected better than OMC.[62] The same workgroup reported that MSX completely abrogated UV-induced DNA fragmentation in a comet assay.[51] In vivo they described a superiority of MSX compared to OMC in preventing tumor formation in mice after UV irradiation.[63] One should notice, however, that all cited studies on MSX activity[51,54,62,63] have been done at the research center of L'Oréal (Clichy, France) who is the manufacturer of mexoryls.

A randomized controlled trial over a 4.5-year period on 1383 adult patients in Australia found a reduced incidence of SCC in the patient group that applied daily a SPF15+ sunscreen compared to the group without photoprotection, but no difference between these two groups in incidence of basal cell carcinomas (BCC).[64] This lack to protect from BCC incidence in adults may be explained by the fact that BCC is probably induced by sun exposure during childhood and adolescence[65] whereas SCC incidence is related to cumulative UV dose including chronic exposure during later phases of life.

The positive or negative role of sunscreens in the development of melanoma has produced major controversy: Some retrospective studies published in the late 1990s concluded that melanoma incidence was higher among sunscreen users and that, paradoxically, sunscreens may induce melanoma.[66-69] These studies were criticized for confounding, e.g., people who are at most risk of burning and most likely to develop melanoma are also most likely to use sunscreens.[70] Two meta-analyses on all data published between 1966 and 2003 did not confirm any relation between sunscreen use and melanoma incidence, neither in positive nor in negative sense.[71,72]

How to explain this confusion? Wavelengths that induce melanoma are not known. The literature emphasizes the role of acute-intermittent sun exposure with sunburn, especially during childhood and adolescence,[73,74] which suggests a role of UVBR in melanoma induction. On the other hand, the augmented melanoma incidence among former PUVA patients[75] demonstrates that UVAR probably also contributes to melanoma initiation. Finally, genetic susceptibility that is not controlled by sun protection habits may play a more important role in melanoma tumorigenesis than previously suspected.

In summary, the to date available epidemiologic data do not prove a protective role of sunscreens against melanoma and BCC, although both tumors are at least partially UV-induced and they show only an incomplete effect against AK, SCC and skin aging. This may have several reasons that are linked under each other:

- The use of sunscreens with insufficient UVB-SPF and lack of coverage in the UVA spectrum: Most data were collected before last generation broad spectrum filters were available. Based on the results of preclinical studies with the new filters, we can expect better protection performance with these sunscreens. But as the time span between UV exposure and skin cancer manifestation in humans is extremely long, incidence numbers will not decrease before several decades.
- The inadequate choice of study population for prospective epidemiologic studies: For both BCC and melanoma, the role of UV exposure especially during the early years of life has been emphasized.[65,74] Studies should therefore focus on protective intervention during this period which makes them yet more difficult to realize as the corresponding tumors arise

about 40 years after critical sun exposure. Gallagher et al reported a randomized controlled intervention trail on white children in which the treatment group that applied a broad spectrum SPF30 sunscreen before each sun exposure over three years developed fewer nevi than the unprotected group. The difference was particularly significant in freckled white children who developed 30% to 40% fewer nevi in the sunscreen-protected group than freckled children assigned to the control group.[76] As high nevus density is recognized as a risk factor of melanoma, this study may indicate a protective potential of broad spectrum sunscreens if they are used regularly during childhood.

- The induction of overexposure behavior by sunscreens protecting effectively against erythema: Autier et al confirmed that sunscreen users usually stay longer in the sunlight than unprotected people.[77] High SPFs suppress the alarm signal of UVB-induced sunburn and induce a false hope of "complete" protection in its users. But DNA damage and photo-immunosuppression are induced already by suberythemal UV doses. Especially if UVA protection of the employed sunscreen is not perfect, overexposure can induce severe photodamage that is not immediately obvious to the sunscreen user.
- The suppression of natural photoprotection mechanisms by the currently marketed sunscreens: Melanine synthesis, release of melanosomes and thickening of stratum corneum are mainly triggered by UVBR that is effectively blocked by modern sunscreens. In the case of repeated sun exposure with a topical photoprotectant having an elevated SPF/PPD (UVB/UVA protection) ratio, the sunscreen user is thus more submitted to the harmful epidermal and dermal effects of UVAR than an unprotected individual who will undergo natural adaptation that protects against both UVBR and UVAR. This is consistent with the observation that people with important chronic UV exposure by occupational outdoor activity, e.g., agricultural workers, who typically have tan and skin thickening in sun-exposed sites, are at a significantly reduced risk of melanoma compared to indoor workers with intermittent UV exposure.[73,74]

Sunscreens and Vitamin D3 Synthesis

Besides its well-known key role in skeletal homeostasis, vitamin D has been reported to have anti-carcinogenic properties. Some studies found an inverse correlation between solar UVB exposure and mortality from cancers, including colon, breast and prostate cancer and between sun exposure and incidence of colon cancer. But these reports failed to eliminate confounding by geographic variations in population genetics or lifestyle behaviors, diet and socioeconomic status of the examined population. Moreover, several other studies did not confirm a role of vitamin D in preventing these cancers (reviewed in ref. 6). An antiproliferative effect for vitamin D is also supported by cell culture and animal model experiments, but the vitamin D concentrations needed to produce these data were generally in the toxic range for humans.

As the cutaneous synthesis of cholecalciferol (vitamin D3) from 7-DHC in cell membranes is exclusively triggered by UVR in the UVB-spectrum (Fig. 1), an interference of high SPF sunscreens with vitamin D3 synthesis seems, at least theoretically, possible. Reduced serum concentration of 25-hydroxyvitamin D has been reported in some persons after regular sunscreen use.[78]

Cutaneous cholecalciferol production is saturated at 10% to 20% of the original epidermal 7-DHC concentration.[79] This threshold amount is achieved by far suberythemal UVB doses in the order of 0.25% DEM to the face and backs of hands 3 times weekly.[6] Additional UVBR transforms previtamin D3 into the biologically inactive metabolites tachysterol and lumisterol.[79] Two prospective controlled studies, one conducted in Australia at a latitude of 37°S with a SPF17 sunscreen and another one done in Spain at a latitude of 41°N with a SPF15 sunscreen, did not find decrease of 25-hydroxyvitamin D serum levels in the protected group compared to the control group, even not in elder individuals of 70 years and older. Secondary hyperparathyroidism and change in markers of bone remodeling were not more frequent in the sunscreen users.[80,81] Another workgroup followed the 25-hydroxyvitamin D serum levels of eight xeroderma pigmentosum (XP) patients who practiced for their severe DNA repair enzyme defect rigorous photoprotection by

avoidance, clothing and sunscreens. Over a 6-year study period, the 25-hydroxyvitamin D serum levels remained in the low normal range with normal levels of PTH and calcitriol.[82] Of course, cutaneous vitamin D3 synthesis may be more difficult in countries at higher latitude than those where the cited studies were conducted, especially in the elder population. On the other hand, housebound elderly are certainly not the principal consumers of sunscreens. For the active population who is continuously or intermittently exposed to sunlight, the given data on the impact of UVB filters on photo-induced vitamin D production does not permit to change recommendation for regular sunscreen use. The actual sunscreen use habits providing only an incomplete protection from UVBR, the remaining UVB exposure seems to be widely sufficient to guarantee cutaneous vitamin D3 synthesis. Moreover, alimentary intake of vitamin D3, e.g., in form of fortified milk or orange juice, can help to maintain sufficient plasma levels.[6] For patients at real risk for vitamin D deficiency, dietary supplementation is efficacious and safe.

Alternative Photoprotective Agents

A great number of substances for topical application have been proposed for photoprotective purpose, e.g., antioxidants acting as radical scavengers, DNA repair enzymes, oligonucleotides stimulating natural melanogenesis, vitamin A derivatives and active botanic components. They have anti-erythemogenic effect and they provided DNA and connective tissue protection in mouse models or in vitro assays after UV irradiation.[7] An anticarcinogenic effect in healthy humans has been described with none of these alternative photoprotectants. Some of them, especially α-tocopherol (vitamin E), L-ascorbic acid (vitamin C) and ferulic acid, are sometimes added to sunscreen preparations. Others are still at an experimental state. In a group of XP patients, topical application of phage T_4 endonuclease V (dimericine) during one year resulted in a 30% decrease of BCC incidence and a 70% decrease of AK incidence.[83] Such significant efficacy of dimericine has not been demonstrated so far in individuals without XP.

Antioxidants have also been tested for photoprotection in oral form. The most currently employed substance is β-carotene with a recommended dose of 120 to 180 mg daily. It diminishes photosensitivity in mild forms of photodermatoses and can moderately increase MED in the healthy caucasian population.[84] This systemic antioxidant may cause cosmetical problems in some individuals by induction of brown-reddish skin color. However, oral β-carotene failed to prevent AK, SCC and BCC in a randomized controlled trial over 4.5 years.[57,64]

Although the photoprotective effects of these alternative agents are promising, their anti-erythemogenic and anti-elastotic action is by far inferior to the one of sunscreens and their efficacy in skin tumor prevention is not established. They may complement the photoprotective activity of sunscreens, but they will probably not replace them as first line photoprotective means.

Discussion and Conclusion

80 years after their commercial introduction, sunscreens remain still most effective for what they have originally been made for, i.e., protection against sunburn and other short-term UV effects such as photodermatoses. They have limited effect in preventing skin aging, AK and SCC. Also in some particular conditions such as genetic disorders or post-transplant iatrogenic immunosuppression that expose to important risk of intermediate-term development of multiple skin cancers, benefit from regular sunscreen use has been clinically established. However, based on this review of clinical and epidemiological data, today's sunscreen formulations cannot pretend to provide protection from nonsquamous cell skin cancer for the general adult population. The genetic part in the etiology of these tumors is not sufficient to explain their still rising incidence worldwide despite wide-spread sunscreen use.

This disappointing lack of efficacy may partially be due to inadequate use of suncare products: Users do generally not apply them for daily short-term outdoor stays and indoor exposure to UVAR traversing window glass, although these conditions are responsible of the major part of cumulative life-time UV dose in the general population having rather indoor occupation. However, non-observance of daily application has been shown to cancel the benefit of sunscreens

in long-term use. Even for planned UV exposure, sunscreens are usually applied in insufficient quantity compared to the protection factor testing conditions which considerably reduces the effective SPF.[44,45] Moreover, users often omit re-application every two hours that is recommended to compensate external product elimination. On the other hand, a consequent and lifelong use of sunscreens in the recommended amounts is not practicable for time and financial expense and safety raisons: In summer 2007, the price of a good quality broad spectrum sunscreen with SPF50+ and an SPF/PPD <2.5 ratio is about 300 €/kg in France. Before sun exposure on the beach, a man with a body surface area of 1.8 m^2 who respects the recommended sunscreen amounts has to apply 36 g for total body protection which causes costs of 10.80 € for only one application. On the other hand, the innocuousness of sunscreen long-term use in the recommended amounts has never been examined with regard to their irritation potential, interaction with toxic substances in the environment, systemic absorption, endocrine activity and clearance.[31] Another reason for sunscreen inefficacy my be the actual use of inadequate efficacy markers for measuring sunscreen protection potency: Both SPF and currently employed UVA-PF markers such as PPD or critical wavelength are not related to photostability, remanence, genome protection and immunoprotection which are however critical parameters for cancer prevention.[85] For the consumer, sunscreen choice is no easy deal: For lack of standardization in UVA protection testing, UVA-PF is often not indicated even for sunscreens with protective activity in this band region. The efficacy of sunscreens is most of all determined by their UV filter composition. But for ingredient lists, the manufacturer can use INCI, IUPAC and trade names of filters which makes it difficult to the user to identify the respective substances. In Europe the consumer is furthermore confronted to confusing multi-language labeling and ingredient lists containing abbreviations in foreign language.

With regard to this review, physicians should omit messages to their patients suggesting that sunscreens can protect from BCC and melanoma. Dermatologists should be concerned to preserve our discipline's credibility in a context where public information is too much dominated by commercial interest of cosmetic and pharmaceutical industry. Sunscreens in their current form are probably not the key to skin cancer prevention in the general population. More basic, but highly effective measures should still be encouraged. This includes sun avoidance especially during peak UVR between 10:00 A.M. and 4:00 P.M., UV-absorbing window filters, photoprotective clothing and wearing broad-brimmed hats. Sunscreens can perfectly complete these recommendations, but they should never cancel them. Much educational work is yet to be done to overcome the popularity of sunbathing and the tanning ideal that are still wide-spread in our society especially in adolescents and young adults. After 30 years, primary and secondary prevention programs now begin to show positive outcomes in Australia, especially in melanoma incidence and survival.[86]

Nevertheless, the benefit of sunscreens against short-term harmful effects of UVR, in cancer prevention in patients with genetic or pharmacological risk of skin tumors and—to a minor degree—even in prevention of skin aging and SCC in the general population is undeniable. Good sunscreen products afford both high SPF and a well balanced SPF/PPD ratio. At the moment, a SPF/PPD ratio of less than 2.5 should be recommended, but in the future even lower SPF/PPD ratios may become possible. Their regular use at least for unavoidable intermittent UV exposure seems to be safe and efficacious. Alternative topical and systemic photoprotectants such as antioxidants and DNA repair enzymes are still at an experimental state in skin cancer prevention.

Major progress has been made during the past 20 years in the sunscreen domain with the development of potent UVA filters, micronization of inorganic sunscreens and synthesis of new photostable and well-tolerated organic filter molecules. These recent sunprotective products will improve the acceptance of sunscreens and thereby the observation of recommendations. They protect us from sunlight probably better than former UV filters that were used in most epidemiologic studies available today on sunscreen efficacy. Considering the slow development of skin cancer in humans, the benefit of our actual sunscreen market will take years to become clinically and epidemiologically obvious. This review will probably have to be revised when the outcome of long-term studies with recent sunscreens will be available.

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