PART III: ACTIVE INGREDIENTS FOR SKIN TREATMENT

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Sunscreens

J. F. Nash and Paul R. Tanner
P&G Beauty, Sharon Woods Technical Center, Cincinnati, Ohio, U.S.A.

INTRODUCTION

There is consensus among the scientific and medical communities that exposure to sunlight is a major factor in the etiology of the progressive unwanted changes in the appearance of skin, i.e., photoaging, and in the risk of skin cancers (1–3). The evidence supportive of this view comes from epidemiology, clinical studies, and experimental studies in humans, laboratory animals, and in vitro systems. It is well established that acute exposure of unprotected skin to ultraviolet (UV) radiation in sunlight produces numerous physiological effects beyond the most obvious which is sunburn (4). Such insults or damage following repeated, lifetime exposure to solar UV lead to skin cancers (5–8), and as presented in Table 1, a myriad of degenerative events responsible for the visible signs of skin aging (10,11). Recent years have seen a very rapid increase in knowledge concerning the etiology and prevention of solar damage (12–14). Since exposure to UV radiation in sunlight is associated with deleterious dermatological events, it is logical that reducing solar UV exposure will diminish such damage to the skin.

Arguably, the complete avoidance of solar UV is neither achievable nor entirely healthy. For example, it is known that exposure to sunlight has health benefits including production of vitamin D (15). As such, moderation seems prudent when considering the balance between the established damage and benefits of solar exposure. To this end, a "safe sun" strategy has been developed and promoted by healthcare professionals worldwide (16–18). An important part of this "safe sun" strategy is the use of sunscreens.

Once the energy from UV is absorbed in the skin, it may produce new chemical entities, e.g., 6′,4′-DNA photoproducts, free radicals, etc., or dissipate the excess energy as heat or phosphorescence. This absorption and subsequent conversion of energy contribute to the processes involved in the etiology of skin cancer and photoaging. Preventing solar UV from interacting with skin chromophores is the primary function of sunscreens. To this end, sunscreen products are quite simple; they absorb/reflect/scatter UV radiation from sunlight before this energy can be absorbed by chromophores residing in the skin. As it turns out, sunscreen products are technically complex. Moreover, such products must be applied to be effective, and as with any other preventative measure, compliance is the key to achieving health benefits.

Table 1 Features of Chronological (Intrinsic) and Photo-Induced Skin Aging

Chronological		Photo-induced	
Clinical	Physiological/histological	Clinical	Physiological/histological
Fine wrinkles	Increase variability in epidermal thickness	Varying degrees of thickness	Epidermal acanthosis
Skin laxity	Decrease in epidermal filaggrin	Coarse wrinkles	Thickened stratum corneum
Dry skin	Reduction in the number of melanocytes	Marked dryness and scaliness	Marked cellular dysplasia
Even skin tone	Reduction in number of Langerhans cells	Uneven pigmentation and lentigines	Variability in size and shape of keratinocytes
Impaired wound healing	Decrease in dermal thickness	Benign, premalignant, and malignant skin lesions	Pronounced flattening of epidermal-dermal junction
	Increase in cross-linkage and disorganization of collagen fibers		Reduction in number of Langerhans cells
	Decrease in number of eccrine, apocrine, and sebaceous glands		Solar elastosis resulting from hyperplasia of abnormal elastic tissue
	Flattened dermoepidermal junction		Blood vessels dilated and on the face called telangiectasias
			Sebaceous gland hyperplasia and pore size

Source: Modified from Ref. 9.

SUNSCREENS

Unquestionably, the safety and efficacy of sunscreen products is of paramount importance. To this end, the function, UV filters, and product design will be discussed.

Function

As stated, the function of sunscreen products is to absorb/scatter/reflect solar UV, thereby reducing the dose of such harmful radiation to the skin. This is accomplished through the use of a combination of UV filters (Table 2) and an appropriate film-forming vehicle. Whereas for most products, such as cosmetics or over-the-counter (OTC) drugs, it might be enough to simply include ingredients that have an established effect, i.e., cough/cold preparations with antihistamines, decongestants, etc., for sunscreens, the protective effectiveness is communicated directly to consumers as the sun protection factor (SPF). Recently, it has been recognized that SPF is incomplete and some additional measure of protection against long wavelength UV, i.e., UVA-I (340–400 nm), is needed. Nonetheless, the SPF is meaningful to consumers and the single most important in vivo measure of sunscreen product efficacy.

For consumers, the most recognized and understood skin response to sunlight exposure is erythema or "sunburn." This can occur in most Fitzpatrick Skin Types and can

Table 2 Approved UV Filters

UV filter	Up to % concentration
Aminobenzoic acid or PABA	15
Avobenzone or butyl methoxydibenzoylmethane	3
Cinoxate	3
Dioxybenzone	3
Homosalate	15
Menthyl anthranilate or meradimate	5
Octocrylene	10
Octyl methoxycinnamate or octinoxate	7.5
Octyl salicylate or octisalate	5
Oxybenzone or benzophenone-3	6
Octyl dimethyl PABA or padimate O	8
Phenylbenzimidazole sulfonic acid or ensulizole	4
Sulisobenzone	10
Titanium dioxide or TiO_2	25
Trolamine salicylate	12
Zinc oxide or ZnO	25

Source: From Ref. 19.

be produced in a clinical setting following exposure to an artificial light source. Most important, the erythema action spectrum, i.e., erythemal response as a function of UV wavelength, is nearly identical to the action spectrum for DNA damage (20–22) and nonmelanoma skin cancer as evaluated in hairless mice and predicted for humans (23). Thus, the current in vivo test used to evaluate the functional efficacy of sunscreens is based on an endpoint that is meaningful to consumers, e.g., sunburn protection, and a surrogate for clinically relevant acute and longer term skin damage.

The SPF is a ratio of the response to solar-simulated UV exposure in protected skin versus unprotected skin. Specifically, the minimum erythema dose (MED) is determined for each panelist in an SPF test. This is the time/dose of solar-simulated UV needed to produce a uniform, barely perceptible redness in the skin. The MED will vary depending on Fitzpatrick Skin Type (24,25). To determine the SPF, a product is applied at a fixed dose of 2 mg/cm^2 over a 50–100 cm^2 area of the lower back. Five to seven "spots" are exposed to varying doses of solar-simulated UV, two/three above, two/three below, and one at the "expected" product SPF. The "expected" SPF is a predicted value from in vitro estimates or the experience of the sunscreen product formulator. At 16–24 hours after UV exposure, the sites are evaluated and the one receiving the lowest UV dose in which a uniform, barely perceptible redness was produced is recorded (26). The "UV-dose/time" is used to calculate the SPF using the following equation: SPF = MED protected skin/MED unprotected skin. According to the methods stipulated by FDA, the SPF is determined in 20 panelists.

There has been much effort to make the SPF test reproducible and reliable, most recently with the introduction of an International SPF Test coordinated by the European Cosmetic Toiletry and Perfumery Association (COLIPA). However, there are several shortcomings of the SPF test and resulting label which should be pointed out. First, it must be clearly understood that the SPF test measures a biological effect using an artificial light source, fixed dose, and an endpoint, i.e., erythema, that is weighted for short wavelengths of UV, namely 290–340 nm (27). Unfortunately, it is overly convenient to refer to SPF as a measure of UVB protection even though it is determined using full spectrum, 290–400 nm, solar-simulated UV and that the UVA-II region (320–340 nm) contributes significantly to high SPF

values. Moreover, because it is a "number," even knowledgeable individuals overemphasize this quantitative index of what is most certainly a qualitative response. For example, an SPF 12 is quantitatively different than an SPF 17, yet from a biological standpoint, the protection afforded by proper use of an SPF 12 or 17 is indistinguishable. As well, the SPF determined under controlled laboratory conditions is dependent on the light source and may be different if the light source changes, e.g., solar-simulated light versus natural sunlight. Finally, the SPF ratio is "nonlinear" since an SPF 15 is not half of an SPF 30 based on the ability to reduce erythemally-weighted UV. That is, the SPF is determined by the erythema action spectrum which, as stated previously, is weighted for short wavelengths of UV. The SPF can be represented as a percent of erythemally-weighted UV transmitted, i.e., 1/SPF $\times$ 100, or blocked, i.e., [1 $-$ (1/SPF) $\times$ 100]. Thus, an SPF 15 blocks 93.3% and SPF 30, 96.7% of the erythemally-weighted UV or a mere 3% difference. Finally and perhaps the most significant limitation of SPF is the failure to provide assurance of protection against long wavelengths of UV, 340–400 nm, or the so-called UVA-I.

Whereas it is now established that protection of long wavelength UVA is essential (28–30), as of December 2005 there is no agreed to, regulatory-mandated means of measuring or communicating UVA protection of sunscreen products to consumers in the United States. To further complicate the situation, there are currently no known surrogates for long wavelength UVA damage that can be measured in the skin following acute exposure to filtered solar-simulated UV. This fact has profound implications for any in vivo human study measuring a UVA protection factor, i.e., the ratio of response to a filtered, artificial light source at a fixed dose in protected versus unprotected skin. The most prominent concern is that any such UVA protection factor based on a response which has no direct relationship to a human health concern, e.g., photoaging or skin cancer, is nothing more than misleading at best. Further, the resulting UVA protection factor is meaningless to consumers since the skin response, e.g., persistent pigment darkening or "color change," is not a response to which protection is considered when purchasing a sunscreen product. Finally, it is possible to measure a UVA protection factor without protecting against the breadth of UVA. Nonetheless, there are numerous proponents of such an approach and tests including persistent pigment darkening (PPD) (31) and protection factor UVA (PFA) (32,33).

Since any in vivo test is without merit, there have been several in vitro methods proposed (34,35). In general, the in vitro approach is based on measurement of absorbance/transmittance of UV through a sunscreen product applied to a substrate (36). The resulting data can be used to calculate a "metric" from which some labeling designation can be derived (37–39). This general approach has been used successfully in several countries including Australia (AS/NZS 2604 Sunscreen products, evaluation, and classification), U.K. (Boots Star Rating), and Germany (DIN draft standard 67502 whereas the UVA-protection is now calculated as UVA-balance). The stated objection to such in vitro approaches is that they are not done on human skin and, as such, cannot provide quantitative information regarding "protection." Despite this concern, substrate spectrophotometric measures of absorption have several advantages including cost, reproducibility, and human subjects are not intentionally exposed to an artificial filtered light source the health consequences of which are unknown. Moreover, the results from in vitro substrate spectrophotometric studies can provide complimentary information to the in vivo derived SPF.

In sum, the function of sunscreen products is to reduce the dose of solar UV thereby mitigating or reducing damage to the skin. The SPF test provides meaningful, in vivo information regarding the protection against solar UV which is weighted for short wavelengths based on the erythema action spectrum. The SPF "number" is recognized by consumers as the measure of sunscreen product efficacy. In vitro substrate

spectrophotometric measures of sunscreen product absorbance and calculation of a metric such as Critical Wavelength can serve as an independent, complementary measure of long wavelength, UVA, sunscreen product efficacy. The American Academy of Dermatology has provided a recommendation (40) which may serve as the basis for a regulatory-mandated testing and labeling for UVA efficacy of sunscreen products.

Active Ingredients: UV Filters

In the U.S., there are 16 UV filters which are approved for use in sunscreen products and are listed in Table 2. Of these 16, there are nine which appear in most currently marketed sunscreen products in the U.S. (41). There is much overlap in the use of such ingredients between U.S. and other regions throughout the world such as Europe (42), the latter having a larger number of UV filters available for use. The human safety of UV filters has been reviewed (39,43–45). In general, the human safety profile of UV filters used in U.S. sunscreen products is favorable based on extensive toxicological data and marketing history. This view is reflected in the appearance of these ingredients on either positive lists in various regions of the world such as Europe and Australia or as Category I ingredients, i.e., safe, and effective, according to the U.S. FDA. Detailed information regarding the human safety of individual UV filters can be found in the review by Nash (39).

The UV filters in sunscreen products are primarily, if not solely, responsible for the absorption/reflection/scattering of solar UV. To achieve the SPF and breadth of UV protection, a combination of UV filters is selected based on their individual absorption profiles and other physiochemical characteristics. For example, to create a sunscreen product with an SPF 15, nearly any combination of UV filters listed in Table 2 can be used. The selection of filters must absorb wavelengths from 290–340 nm to achieve the desired SPF 15. If protection against long wavelength UV is to be achieved, then in the U.S. the options are much more limited. Specifically, one must select either avobenzone or zinc oxide, both of which absorb long wavelength UVA-I (340–400 nm). As the SPF of the product increases so too does the concentration and number of UV filters. This is represented in Figure 1. The percent concentration of UV filters in a hypothetical SPF 15 product ranges from 10–15% and for an SPF 45, up to 30% and beyond. Net, the higher the SPF, the higher the concentration of UV filters.

Products

UV filters are the functional component of sunscreens while the formulation is the "art." The general goal in formulating modern sunscreens is to design the best product that meets the desired UV efficacy targets of SPF, UVA/broad spectrum protection, and substantivity, i.e., water/wear resistance. Typically, the best product is the one that most effectively manages factors such as cost, skin compatibility, and aesthetics/skin feel (46).

From an ingredient standpoint, most sunscreen products are typically very similar to conventional lotions or creams, with the key difference being the addition of 4% to 40% sunscreen actives (Fig. 1). From a formulation perspective, the current list of UV filters (Table 2) can be categorized into one of four groups based on the physical properties of the active:

- Polar oils, e.g., octinoxate, octisalate, homosalate, and octocrylene
- Oil soluble crystalline solids, e.g., avobenzone, and the benzophenones
- Water soluble salts, e.g., ensulizole
- Insoluble powders/particulates, e.g., zinc oxide and titanium dioxide

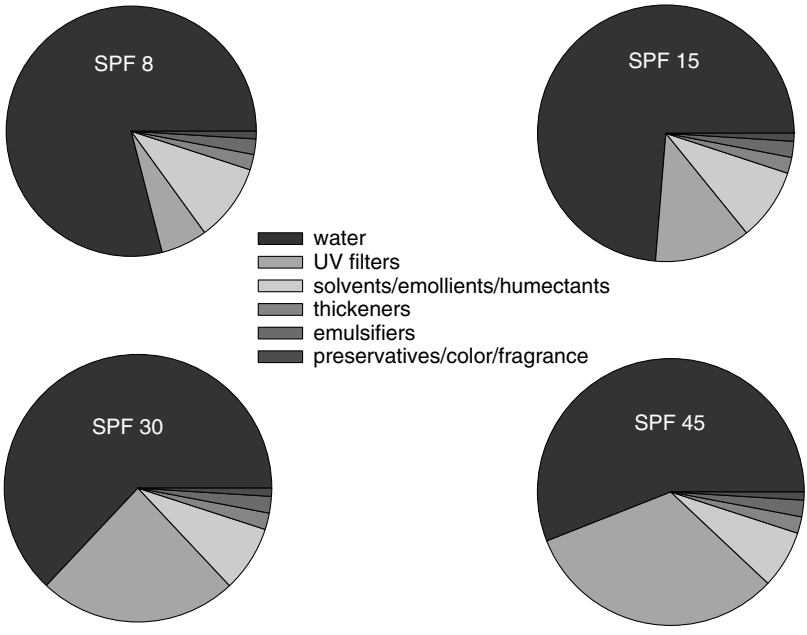

Figure 1 Hypothetical sunscreen products ranging from SPF 8–45. As the SPF increases the percent of UV filters increases.

Importantly, given the concentration of UV filters used in sunscreen products, i.e., up to 40% for high SPF products, and their physical properties, by far the greatest factor involved in managing cost, skin compatibility, and aesthetics/skin feel in formulating new sunscreen products is the selection and combination of these sunscreen actives.

Cost

Current sunscreen actives are expensive relative to the key ingredients utilized in most lotion and cream vehicles, typically ranging from $10 to $100 per kilogram. Thus, the higher the level of sunscreen actives in a formulation, the greater the formula cost, and hence the more marketers charge for the product. In turn, and perhaps as a direct consequence, one might expect that the more expensive the sunscreen product the more sparingly, i.e., lower dose and reduced frequency, it will be used by consumers (47).

Skin Compatibility

Along with fragrances and dyes, UV filters, particularly organic moieties, are known to elicit irritant responses in subjects predisposed to such skin reactions (48,49). It is generally desirable, therefore, to reduce to a minimum the concentration and number of UV filters present in a sunscreen product formulation to minimize risk of these types of incompatibilities.

Aesthetics/Skin Feel

Each type of sunscreen active described above can have a negative impact on sunscreen product skin feel, with higher levels having a corresponding larger effect. Specifically, the general skin-feel tradeoffs of the various types of sunscreen actives are:

- Polar oils tend to make the product feel greasy and oily, especially at high concentrations.
- Oil soluble crystalline solids require high levels of oily solvents/emollients to dissolve them and keep them from crystallizing in the product over time, and hence make the product feel greasy and oily.
- Water soluble salts tend to reduce the capability of most aqueous polymeric thickeners. This, in turn, leads to the use of much higher polymer levels to achieve a target product thickness, and these high polymer levels make the product feel sticky and heavy on the skin.
- Insoluble powders/particulates can make the product feel dry and draggy, and often can lead to an undesirable white appearance on the skin.

Additionally, even beyond the specific aesthetic effects above, there is a further general effect that comes from putting significant levels of sunscreen actives into a product—higher "coated" feel on the skin. Specifically, the single largest component of most non-sunscreen lotions and creams is a volatile carrier, typically water. Thus, when a layer of non-sunscreen lotion or cream is applied to the skin, most of the product evaporates, leaving behind a thin layer of non-volatile material consisting of moisturizers, emollients, thickeners, preservatives, and similar materials. By adding UV filters to a formula to achieve SPF 15 or SPF 30, for example, the level of volatile carrier in the product is significantly reduced. As a result, much more of the applied product is left behind on the skin, and the skin feels "coated." Thus, even if the greasy, draggy, or sticky effects of the sunscreen actives are reduced by other technologies, the skin will still be left with an unpleasant coated feeling given the high level of non-volatile materials left behind from the sunscreen product. To compensate for this, many consumers apply product at a lower dose or less frequently, which will likely reduce the efficacy (50,51).

As stated, all of these factors—cost, skin compatibility, and aesthetics/skin feel—will influence patient compliance, either directly, viz amount of product applied and frequency of application/reapplication, or indirectly in decisions related to repurchasing the product. Thus, by developing more efficient sunscreens, manufacturers can minimize the amount of sunscreen actives needed to achieve a given efficacy target, and hence deliver lower cost, less irritating, and better-feeling sunscreen products. Sunscreen products consumers will use more regularly will provide a significantly greater degree of protection.

SELF-TANNING PRODUCTS

The health and beauty of a "tan" has been ingrained in a generation of westerners (52). Unfortunately, this fashion image is diametrically opposed to the message being promoted by healthcare professions, namely to avoid sunlight or other artificial UV light sources, e.g., tanning salons, which is primarily responsible for the beautiful tan. Attempts have been made to provide "color" or artificial tans without intentional exposure to solar or solar-simulated UV. The most successful of these self-tanning products are the ones which containing dihydroxyacetone (DHA). These self-tanning products impart color to the skin which is temporary and may be a safer approach toward achieving a "tan" (53).

Function

As stated, the function of self-tanning products is to temporarily impart color to the skin. Darkening of the skin occurs in response to solar or solar-simulated UV exposure which is

the body's natural response to UV exposure. Melanogenesis is a very complex process that is still not fully understood (54,55). It is the image of beauty and health to sport a "tan," and whereas the public health message to avoid intentional solar exposure has had some small impact, there has been an increase in the use of tanning parlors (56,57). Importantly, there are individuals who will engage in risky behavior regardless of the costs/consequences. As such, the use of sunless tanning products may provide an important alternative for some.

An artificial "tan" resulting from the application of a DHA-containing product does provide some limited, short-lived protection against UV (58–60). More recently, it has been reported that topical application of DHA to hairless mice will delay UV-induced photocarcinogenesis (61). These protective benefits are promising as sunless tanning gains in popularity.

Ingredients

Most, if not all, commercial sunless tanning products utilize DHA to deliver a tanned appearance to the skin. Dihydroxyacetone is a three-carbon sugar that reacts nonenzymatically with amino acids in the outer layers of skin to produce brown/tan colored polymers (62). This color-forming reaction, i.e., the Maillard Reaction, is not immediate, and hence visible tanning is not noticeable until a few hours after application. Further, the tanned color produced by DHA is substantive, lasting several days before it gradually fades away as the outer layers of skin cells slough away. This is in contrast with common bronzing products that provide immediate color to the skin through the use of dyes and colored pigments that can be easily washed off. In addition to DHA, several sunless tanning products also contain erythrulose (63), another sugar capable of reacting with skin proteins to generate a more even and longer lasting sunless tan.

Products

The goal of a sunless tanning product is to deliver DHA to the skin in a way that provides an even, natural looking tan color (64). To achieve this, there are three important considerations. First, the formulation must ensure that the DHA itself remains stable; otherwise, the product will develop an unpleasant brown color and burnt caramel off-odor in the package, and the sunless tan provided by the product will be compromised. Stability is achieved, for example, by a combination of an optimal product pH and avoiding materials in the formula that react with DHA, such as amine functional materials and certain pigments.

Second, the product needs to spread the DHA very uniformly on the skin to provide an even, streak-free tanned color. To achieve good spreading, a number of new product forms beyond traditional sunless tanning lotions have been introduced, including sunless tanning sprays, foams (mousses), and wipes. Finally, the sunless tanning product needs to absorb into the skin and dry quickly, to make it easier and more convenient to achieve a good tan. Getting dressed or going to bed while a sunless tanning product has not fully absorbed into the skin can lead to uneven color as well as stained fabrics. Thus, creating faster absorbing/drying sunless tanning formulas, like the sprays and foams mentioned above, ensures best results.

Importantly, while all of this sunless tanning product technology has yielded significantly improved sunless tanning products over the early sunless tanning products of 20-plus years ago, the reality is that achieving a good, even sunless tan still depends a great deal on factors other than the product. For example, proper skin preparation via cleansing

and exfoliation is critical to achieving an even, lasting sunless tan. Also the reaction between DHA and the skin takes several hours. Avoiding sweating, swimming, or showering for several hours after product application is also important to ensure best results. Finally, since DHA tends to more intensely color skin that has thicker, more compact outer layers, it is important to wash the hands after applying product to avoid dark brown stained palms.

FORMULATION CHALLENGES

Given the potential cost, compatibility, and skin feel benefits of increased sunscreen efficiency, there have been a number of technologies developed in the past 10-plus years to improve sunscreen products. For example, the use of film formers, better wetting/spreading emollients, and shear-thinning rheology modifiers allow sunscreen products to spread more evenly and form a uniform film on the skin. A more uniform film leads to increased UV efficacy/efficiency by effectively reducing and/or eliminating "holes" in the product film. The use of combinations of UV filters in both the water and oil phases of emulsions provide increased efficacy/efficiency by ensuring that there are no unprotected areas in the product film. Another example is the identification/development of photostable sunscreen active combinations which allows lower concentrations of UV filters to be used to achieve a UV efficacy target. For systems that are not photostable, much higher concentrations of UV filters are needed to compensate for the loss of UV efficacy that occurs during product exposure to UV on the skin. Finally, the development of newer, more efficient and more photostable UV filters allows formulators to achieve a target UV efficacy with less sunscreen active. Reducing the concentration of UV filters may improve the product aesthetics with the potential for increasing compliance.

Improving Sunscreen Product Aesthetics

Based on the above discussion, the first and simplest strategy for modern sunscreen formulation must be to use a lower concentration and number of UV filters to achieve the target UV efficacy level or, in other words, identify the most efficient sunscreen systems. Beyond this, there are other approaches that are often utilized to manage the trade-offs of the various sunscreen actives. These include:

- The use of cosmetic powders to reduce the greasiness of the oily UV filters or solvents. These powders can absorb oily materials and give the product a drier skin feel.
- Adding oil-soluble film-forming polymers to thicken the oily sunscreen actives and solvents/emollients, thus reducing slick/oily/greasy feel on the skin. Such polymers are also important as they increase the efficiency/efficacy of the sunscreen product by improving uniform skin coverage or film.
- Incorporating silicone emollients to reduce the draggy, dry skin feel of zinc oxide and titanium dioxide sunscreen actives.
- Utilizing alternative product forms to minimize product skin feel negatives, such as using rub-free sprays.

It is these types of technologies, driving efficiency and promoting aesthetics, which have given birth to the new generation of sunscreens, allowing even products with SPF greater than 15 to be formulated as recreational as well as daily use products such as

moisturizers. Importantly, these optimized sunscreen products can have excellent aesthetics that improve compliance and afford greater protection.

REGULATORY ISSUES

In the U.S., sunscreen products are regulated by the Food and Drug Administration (FDA). Specifically, sunscreens are considered OTC drug products, required to abide by the monograph regulating such products. The OTC Drug Monographs establish conditions for safe and effective self-treatments. These are regulatory standards for marketing of non-prescription drug products not covered by New Drug Applications (NDAs). Products marketed in accordance with the monograph do not require FDA approval. An abbreviated chronology of the Sunscreen Monograph is presented in Table 3.

That sunscreens are considered drugs in the U.S. sets it apart form other regions of the world. The FDA considers cosmetics as "… articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance." In 1978, the FDA recognized that products intended to be used for prevention of sunburn or any other similar condition should be regarded as drugs. As such, in the Advanced Notice of Public Rule Making (ANPRM) it states that "[sunscreens] reduce by varying amounts the solar radiation absorbed by the skin and thereby affect the physiological response and extent of the erythemal reaction (redness) produced …" and as such fit the definition of a drug: "articles (other than food) intended to affect the structure or any function of the body of man or other animals."

Since the publication of the ANPRM in 1978 up to the publication of the Final Rule in 1999 (19) and beyond for a total of 27-plus years, the Sunscreen Monograph has been discussed and commented on by interested parties including industry, academicians, practicing dermatologists and various trade associations (65). There has been extraordinary criticism of the agency ranging from being too slow to completely unresponsive. Perhaps the critics are right. However, it should be noted that there are diverse opinions on many key aspects of sunscreens including product testing and labeling, the knowledge that consumers don't apply enough product to achieve the labeled SPF, the absence of any meaningful and relevant acute endpoint for UVA protection, the need for sunscreens with unlimited SPF, i.e., beyond 100-plus, and what exactly such products are protecting against. This is compounded by the fact that there are sharp disagreements regarding how best to measure and label sunscreen products (see Sept. 2000 submissions to the FDA Sunscreen Docket 78N-0038). As such, it may not be surprising that the monograph has not been completed.

Beyond the monograph, there are other regulatory processes that can be followed in order to market a sunscreen product in the U.S. Options for marketing an OTC drug product besides the monograph include NDAs and the Abbreviated NDA (ANDA). An NDA is the same process that prescription drugs follow including the comprehensive safety and clinical testing. Approval is generally for a specific product including the 10–20 or so ingredients used to formulate a topically applied product. As such this approach is time consuming and costly and does not allow for minor reformulations of the product for marketing or other reasons. There are few sunscreen products which follow this process given the high cost in time and resources and the inflexible nature of this process.

Currently, there are several suppliers attempting to have specific UV filters added to the list of approved ingredients (Table 2). The Time and Extent Application (TEA) is being used. The purpose of TEA is to request that applicable conditions be considered for

Table 3 Abridged Chronology of FDA Sunscreen Monograph

Federal register (FR) notification	Date
Pursuant to the notice published in the FR requesting the submission of data and information on OTC topical sunscreen drugs	Dec 1972
Advisory review panel reviewed ingredients, claims, labeling, dosage, and warnings	
Advanced notice of proposed rule making (ANPRM)	Aug 1978
Establish conditions for the safety, effectiveness, and labeling of the OTC sunscreen drug products	
ANPRM—Extension of comment period (FR) to Dec 15, 1978	Dec 1978
Docket officially closed Dec 26, 1978	
Administrative record reopened	March 1980
FR announcement of public meeting held on Jan 26, 1988	Sept 1987
FR extended comment period for test procedures and related claims	May 1988
Tentative final monograph (TFM)	May 1993
Reflects tentative adoption of the ANPRM on the basis of the comments received and agency's independent evaluation	
FR announced public meeting to discuss UVA claims and testing	April 1994
FR amend TFM and reopen comment period	June 1994
FR announced a public meeting to discuss the photochemistry and photobiology of sunscreens	Aug 1996
FR amendment to TFM to include avobenzone	Sept 1996
Interim marketing was allow according to FR, April 1997	
FR amendment to TFM to include zinc oxide	Oct 1998
Final rule—sunscreen products monograph	May 1999
Completes the TFM except for certain testing issues such as UVA testing and labeling, which will be addressed later. UVA labeling may continue in accord with the TFM and its amendments	
FR extended effective date to Dec 2002 and reopened administrative record for public comment until Sept 2000	June 2000
FR suspended final rule indefinitely until comprehensive monograph developed	Dec 2001
FR technical amendment updates to incorporate USP names for four active ingredients, effective Sept 2002	June 2002

inclusion in the monograph. This is a two-step process: first is the submission followed by demonstration of general safety and effectiveness. The demonstration of general safety and effectiveness has, to date, been the limiting factor for TEAs.

Whereas the debate regarding sunscreens being cosmetics or drugs and the criticism of the Sunscreen Monograph and FDA will continue, it again is worthwhile pointing out that in the U.S. such a process works by necessity if nothing else.

SAFE SUN STRATEGY

Skin cancers and photoaging/chronic skin damage are recognized as consequences of solar UV exposure by government agencies and numerous professional organizations. These groups recommend strategies to reduce solar UV exposure (Table 4). Chief among the recommendations of any safe sun strategy is the use of sunscreen products.

American Academy of Dermatology (http://www.aad.org/)

The American Academy of Dermatology's Guidelines/Outcomes Committee has developed "Guidelines of Care for Photoaging/Photodamage." In these guidelines the committee states, "No credible scientific evidence contradicts the relation of sun exposure to the development of skin cancer and the undesirable results of photoaging and photodamage." The committee contends that a significant portion of the approximately $14 billion spent on cosmetics in the U.S. in 1996 was specifically spent to conceal the effects of photoaging and photodamage. An additional significant amount of money is spent on surgical and medical procedures. The committee believes that early recognition and treatment of photodamaged and photoaged skin will lead to a decrease in the incidence of premalignant and malignant skin lesions.

- Photodamage and photoaging are at least partially reversible with photoprotection, and the use of sunscreens that protect against solar UV is encouraged.

American Cancer Society (http://www.cancer.org)

In its efforts to educate the American public about the importance of prevention and early detection of nonmelanoma and melanoma skin cancers, the American Cancer Society discusses on its Web site the damage that UV can cause to skin and eyes, including the effects of photoaging.

The short-term results of unprotected exposure to UV rays are sunburn and tanning. The long-term effect of such damage is more serious. UV exposure that is intense enough to cause sunburn clearly increases the risk of developing skin cancers. And UV exposure can increase skin cancer risk even without causing sunburn. Long-term exposure can also cause premature changes in skin including:

- Aging
- Wrinkles
- Loss of elasticity
- Dark patches (lentigos, that are sometimes called "age spots" or "liver spots"
- Actinic keratoses.

Skin Cancer Foundation (http://www.skincancer.org/)

The Skin Cancer Foundation recently updated its brochure, "Simple Steps to Sun Safety," which states:

- Your skin is an excellent record keeper. Every moment in the sun adds up, accumulating like money in the bank. The payoff, however, is damage to the skin

Table 4 Safe Sun Guideline Practices

Minimize exposure to solar UV radiation, especially between the hours of 10:00 am and 3:00 pm DST
Wear protective clothing (e.g., wide-brimmed hats, sunglasses, long-sleeved shirts, and pants)
Always use sun protection while outdoors, including when near snow, water, sand, and at high elevations
Avoid artificial tanning devices, such as tanning booths and sunlamps
Use the UV index when planning outdoor activities
Apply sunscreens with an SPF greater than or equal to 15 daily

and possibly skin cancer. … Sunlight also causes wrinkling, blotching, drying, and leathering of the skin, making you look old before your time. The best defense, now, and for the future, is to limit time in the sun and protect yourself whenever you go outdoors.

American Society for Photobiology and European Society for Photobiology (http://www.pol-us.net/)

The American Society for Photobiology (ASP) is also "concerned with the interaction of light and living things" including the harmful effects of UV on humans. In its publication the *Light and Life* brochure, published "to inform government officials, students, and the general public about the science of photobiology," the ASP states:

- *Harmful effects of light*. Sunlight is implicated in several skin diseases, including premature aging of the skin and skin cancer. Skin sensitivity to sunlight is controlled by the genetic ability of an individual to produce melanin, the pigment that helps protect the skin from light-induced injury.
- *Photoprotection*. Both topical and systemic sunscreen agents prevent the acute and chronic effects of sunlight. They enable people to work outdoors and enjoy outdoor activities with reduced risk of sun-induced injury. The damage that absorbed light creates in the skin, such as the changes recognized as aging of the skin, is preventable by using new types of water- and sweat- resistant sunscreens.

Centers for Disease Control and Prevention (http://www.cdc.gov/)

The Centers for Disease Control and Prevention (CDC) has educational programs and recommendations that are targeted to apply "disease prevention and control, environmental health, and health promotion and education activities designed to improve the health of the people of the United States." On its Web site "Choose Your Cover," it specifically states:

- …excessive and unprotected exposure to the sun can result in premature aging and undesirable changes in skin texture. Such exposure has been associated with various types of skin cancer, including melanoma, one of the most serious and deadly forms.

National Institutes of Health/Environmental Protection Agency (http://www.nih.gov/)

In addition to the CDC, other government agencies including the National Institutes of Health (NIH) and the Environmental Protection Agency (EPA) have reiterated concern about the effect of UVA on the skin. The "MEDLINEplus Health Information" service of the U.S. National Library of Medicine and the National Institutes of Health states that

- …[s]unscreens help to prevent sunburn and reduce the harmful effects of the sun such as premature skin aging and skin cancer.

The EPA has related materials on its Web site to promote greater public awareness of the impact of UV exposure:

- Exposure to UV radiation from the sun can seriously harm human health. Mild exposure can lead to sunburn. More extended exposure to the sun may result in premature aging and discoloration of the skin and, ultimately, skin cancer. These

> health effects have only been made more acute by the destruction of the ozone layer which protects the earth from the sun's UV radiation. … The EPA and other agencies also promote awareness of the dangers of sun exposure and the safety precautions such as minimizing exposure and using sunscreen.

CONCLUSIONS

Given the potential health benefits of sunscreens, it is perhaps not surprising that they have been referred to as the "ultimate cosmetic" (66). It is clear that exposure to solar UV damages human skin. This can be in the form of acute over-exposure resulting in sunburn or more subtle subclinical damage. In either case, repeated exposure to solar UV manifests as photoaging and skin cancers after many years. The molecular mechanisms of skin cancers and photoaging have been studied using human and animal models. More important, use of sunscreens protects against short-term markers of UV-induced skin damage and the molecular events believed to be responsible for skin cancers and photoaging. That is, based on experimental investigations, sunscreens or UV filters reduced molecular, biochemical, and clinical events associated with skin cancer and photoaging.

An international meeting with experts from around the world concluded that sunscreens were probably of benefit in reducing squamous cell carcinoma but there was not enough evidence supportive of protection against basal cell or melanoma skin cancers (67,68). Prospective clinical studies in areas of high incidence such as Australia (69,70) and Texas (71) clearly show the benefits of regular application of sunscreens. Demonstration of such effects in these relatively short duration studies, i.e., less than five years, are if nothing else encouraging.

The formulation of sunscreen products should be focused on improving compliance rather than increasing the Protection Factor of products. It is easy for sunscreen manufacturers to get caught up in the SPF horsepower race since consumers may purchase product based on the SPF number and physicians may recommend/prescribe products thinking that sunscreens are not applied at the proper dose and, as such, a higher SPF will compensate for this underdosing. However, as with any preventive therapy, compliance is the key and making products which are applied at the proper dose and reapplied should be the goal of manufacturers.

Also, sunscreen products need to protect against the breadth of solar UV and not simply short wavelengths. Presently, consumers purchase products which infer protection against harmful rays of the sun, i.e., SPF. As discussed, this does not ensure any protection against long wavelength UVA-I. Arguably, sunscreen manufacturers should *only* market products which protect against the breadth of solar UV. In the U.S., the FDA could ensure all products sold meet or exceed a single criteria to achieve a "broad spectrum" label such as recommended by the AAD (40) thereby ensuring consumers are fully protected by the sunscreen products purchased.

The public health message endorsed by numerous governmental and academic groups is that of a "safe sun strategy," which includes the daily use of a sunscreen at least SPF 15. It will be important to maintain this basic message and expand it to include sunscreen products that provide "broad spectrum" protection. This could be achieved by regulatory adoption of, and in vitro substrate spectrophotometric measure of UVA efficacy and a simple pass/fail label. As such, consumers could choose products which protect against the solar UV spectrum.

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10

Photoprotection and the Prevention of Photocarcinogenesis

Nathalie Nguyen and Darrell S. Rigel
Department of Dermatology, New York University School of Medicine, New York, New York, U.S.A.

OVERVIEW

Exposure to ultraviolet (UV) energy leads to two significant types of skin problems—increased risk for the development of skin cancer and accelerated photoaging changes. At current rates, one in five Americans will develop a skin cancer of some sort during their lifetime, with over 1,000,000 new cases appearing this year alone in the U.S. The incidence of malignant melanoma is increasing faster than any other cancer in the United States. In 1935, the lifetime risk for an American developing invasive melanoma was one in 1500. In 2005, this risk was one in 62 for invasive melanomas and one in 34 if in situ melanomas are included. In addition, according to the World Health Organization, melanoma is increasing faster than any other malignancy worldwide. The economic magnitude of this public health problem is illustrated by the fact that costs associated with the treatment of skin cancers are over 500 million dollars annually in the U.S. alone (1). Therefore, the development and implementation of effective mechanisms that protect the skin from cancer-causing UV rays is critical.

Photoprotection is therefore focused on protecting the skin from the damage that occurs as a result of UV exposure. The approach to photoprotection focuses on a reduction in the overall exposure to sunlight, not to just a single component of it. To put the importance of photoprotection and skin cancer into perspective and to better understand the key associated issues, one needs to appreciate:

- The relationship of skin cancer and UV exposure
- Why recent changes have made this issue even more important,
- Current available agents and approaches,
- How effective these approaches are and can be,
- What can be done in the future to improve photoprotection effectiveness, and,
- What clinical recommendations can be made to patients to lower their future risks for photoaging and skin cancer.

Increasing awareness of the damaging effects of sunlight has led to an increased need for adequate photoprotection. Primary prevention to reduce the incidence of skin

cancer therefore includes a regimen consisting of effective sunscreen, protective clothing, and behavior modification.

RELATIONSHIP OF UV EXPOSURE TO SKIN CANCER DEVELOPMENT

The skin is the most exposed organ to environmental UV and to the associated sequellae (2). Exposure to UV radiation on the skin results in clearly demonstrable mutagenic effects. The p53 suppressor gene, which is frequently mutated in skin cancers, is believed to be an early target of UV radiation-induced neoplasm (3). Although there is no direct way that the active wavelengths for the development of skin cancer in humans can be determined, there is ample indirect evidence demonstrating probable ranges. In terms of SCC in albino hairless mice, the action spectrum has been determined to have a strong peak at 293 nm with secondary peaks at 354 and 380 (4). The primary wavelength influencing melanoma risk appears to be in the Ultraviolet B (UVB) (290–320 nm) range. However, studies in fish and opossums have also shown an increase in melanoma development when exposed to UVA wavelengths (5,6). Fair skinned individuals who are more sensitive to the effects of exposure at these wavelengths are at higher risk for the development of skin cancer (7). In addition, skin cancer rates are also elevated in persons with increased artificial UV exposure through tanning salons (8).

The amount of average annual UV radiation correlates with the incidence of skin cancer (9). There is a direct correlation with BCC and SCC incidence and latitude (10). Scotto et al. (11) demonstrated a strong inverse correlation between latitude and incidence of BCC and SCC for both men and women.

In terms of melanoma, the relationship is not as clear-cut. Incidence rates for melanoma correlate in a lesser way with latitude as that for NMSC but other factors may also be involved (12). Melanoma mortality rates in the U.S. and Canada have also been shown to directly correlate with ambient UV exposure (13). The correlation of melanoma incidence to UV radiation exposure is greater when ambient UVA (320–400 nm) radiation is also included (14). High-altitude regions tend to have a higher melanoma rate that may be related to the higher UV fluences noted at these sites (15). Melanoma risk has also been noted to be directly related to annual UV flux. Fears et al. (16) demonstrated that when lifetime residential history was coupled with levels of midrange UV radiation (UVB flux) to provide a measure of individual exposure to sunlight a 10% increase in annual UVB flux was associated with a 19% increased risk of melanoma. Even in women who could develop a deep tan, a 10% increase in hours spent outdoors was associated with 5.8% increase in melanoma incidence. The association between melanoma risk and average annual UVB flux was strong and consistent for men and women. However, some of the studies examining a latitudinal gradient for melanoma risk have been somewhat inconclusive (17). Although worldwide studies have only shown a weak correlation, the association of melanoma mortality in 1950–1967 with estimates of annual erythemal solar UVB dose across the U.S. and Canada demonstrated a stronger relationship (18).

The anatomic areas that skin cancer develops on appear to be somewhat related to the average amount of UV exposure to those sites (19). The density of skin cancer is highest on the sites that are virtually constantly exposed to UV, namely, the head and neck. Skin cancer rates are low in rarely UV-exposed areas such as the scalp in women and the buttocks in both sexes (20). Melanoma tends to be found more frequently in women on the legs where more average UV exposure may occur than in men (21).

The timing and periodicity of the UV exposure appears to be important in its effect on subsequent skin cancer risk. In terms of NMSC, the long-term chronic UV exposure

appears to increase the chance of developing this cancer. Acute intermittent UV exposure elevates subsequent melanoma risk (22). Migration studies have demonstrated sun exposure early in life appears to have a greater influence on subsequent skin cancer risk than does that at a later age. Persons born in the high-UV insolation environment of Australia have a increased risk for developing skin cancer compared to those born in Northern Europe who migrated at age 10 or older (23). Several additional studies from other countries have also found that risk of developing melanoma was less in those who migrated to the country 10 or more years after birth than were those who were born there (24,25). However, a recent study has now demonstrated that excessive UV exposure later in life may be equally important to that acquired earlier. Pfahlberg et al. (26) found a very similar upward gradient of melanoma risk in exposure categories related to the frequency of sunburns comparing UV exposure occurring before and after age 15. More than five sunburns doubled the melanoma risk, irrespective of their timing in life. This study did not provide supporting evidence for the existence of a critical age interval but rather suggested that the hazardous impact of UV exposure seems to persist lifelong.

SPECTRAL DIFFERENCES RELATED TO UV PHOTOCARCINOGENESIS

Most of the cutaneous damage resulting from radiation exposure occurs from the UV band. The shortest of the UV rays, UVC (100–280 nm), fail to penetrate the earth's ozone layer and thus exert little damage. UVB (290–320 nm) is responsible for most of the cutaneous changes induced by exposure to the sun. Known biochemical changes induced by UVB include alterations in DNA, RNA, and protein synthesis, induction of cyclobutyl pyrimidine dimers, and production of various cytokines (27,28).

In the past, UVA was believed to play less of a role in the pathogenesis of skin cancer and sun damage. The longer wavelengths of UVA (320–400 nm) allow deeper penetration into the skin. UVA induces an immediate pigment-darkening reaction and new melanin pigment formation (29). Earlier sun protection focused primarily on eliminating UVB exposure to the skin. UVA is now known to contribute to skin cancers by inducting DNA mutations directly as well as by augmenting damage incurred by UVB (30). Human skin exposed to UVA has altered expression of the p53 tumor suppressor protein (31). These mutations can be reduced by using UVA sunscreens, demonstrating that there is less p53 accumulation with better UVA protection (32).

PHOTOCARCINOGENESIS-DECREASING PHOTOPROTECTION MODALITIES

Protection from exposure to UV radiation leads to decreased risk for developing skin cancer. The use of multiple modalities leads to overlapping and more comprehensive spectral coverage. Therefore, optimal photoprotection includes regularly using sunscreen, wearing protective clothing, and avoiding UV exposure where possible. Recommendations for photoprotection which include all three of these approaches should be most effective in reducing skin cancer risk.

SUNSCREENS

Sunscreens work primarily through two mechanisms: (i) scattering and reflection of UV energy, and (ii) absorption of UV energy. Many current sunscreens contain ingredients that work through both mechanisms in terms of UV protection.

The most important assay for determining the effectiveness of a sunscreen is the sun protection factor (SPF). The SPF measures a sunscreen's ability to prevent development of erythema upon exposure to UV radiation, primarily UVB. The SPF value is defined as the ratio of the UV energy required to produce minimal erythema on protected skin to that required to produce the same erythema on unprotected skin in the same individual. For example, an individual using a sunscreen SPF 4 will take four times as long to develop cutaneous erythema when exposed to UVB radiation, as compared to when that individual has no protection. The Food and Drug Administration (FDA), which oversees the marketing and distribution of sunscreen products in the United States, mandates that a sunscreen agent must provide at least an SPF value of 2. Most commercially available sunscreen products have SPF values that exceed the minimum protection.

Despite attempts by the FDA to educate consumers and promote appropriate branding by manufacturers, sunscreen labeling has its limitations. The complicated names, as well as the variations in names for any given agent, may be overwhelming for the average consumer. The photostability of sunscreens is not quantified or labeled, and varies according to the chemical agent. The SPF value primarily measures a sunscreen's ability to protect against UVB radiation and does not adequately address the effects of UVA. In addition, SPF readings may also vary for a given agent depending on the light source (33).

Nonetheless, concerted efforts to educate consumers have been the goal of the FDA. Confusing terminology such as "sunblock" and "all-day protection" is prohibited. The term "waterproof" should be replaced with "water resistant." The FDA discourages the branding of a sunscreen product as having an SPF of greater than 30. Although values greater than 30 offer increased protection, the risks of providing consumers with a false of security encouraged the labeling to restrict labeling to 30-plus. For sunscreen products making the claim of "water resistant," the label SPF is the SPF value determined after forty minutes of water immersion, as determined by FDA guidelines.

TYPES OF SUNSCREENS AND MECHANISMS OF ACTION

Sunscreen use began in the early 20th century. Salicylates were the first agents used in sunscreen preparations, with the first reported sunscreen containing benzyl salicylate and benzyl cinnamate (34). In the 1940s, p-Aminobenzoic acid (PABA) was patented and incorporated into sunscreen formulations (35). Since its debut, various formulations and derivates of PABA have been introduced into the sunscreen market. Today, the FDA approves the use of 16 chemicals as defined sunscreen agents (Table 1).

Since no single agent effectively provides adequate protection from both UVA and UVB radiation, nearly all commercially available sunscreen products contain agents from both groups. Two or more sunscreen active ingredients may be combined with each other in a single product when used in the concentrations approved by the FDA for each agent. Each individual active ingredient must contribute a minimum SPF of at least 2 to the finished product, with the finished product having a minimum SPF of not less than the number of sunscreen active ingredients used in the combination multiplied by two. Sunscreen agents are classified based on their method of protection. Chemical sunscreens

Table 1 FDA-Approved Active Ingredients for Sunscreens

Ingredient	UV absorbance
Aminobenzoic acid	UVB
Avobenzone	UVA
Cinoxate	UVB
Dioxybenzone	UVA, UVB
Homosalate	UVB
Methyl anthranilate	UVA
Octocrylene	UVB
Octyl methoxycinnamate	UVB
Octyl salicylate	UVB
Oxybenzone	UVA, UVB
Padimate O	UVB
Phenylbenzimidazole sulfonic acid	UVB
Sulisobenzone	UVA, UVB
Titanium dioxide	Inorganic
Trolamine salicylate	UVB
Zinc oxide	Inorganic

Source: From Ref. 36.

absorb UV radiation while physical blockers act as particulate matters that reflect and scatter incident light.

CHEMICAL SUNSCREENS

Chemical sunscreen agents protect the skin by absorbing UV energy and transforming it into heat energy. These compounds absorb UV radiation and convert the energy into longer wave radiation. The sunscreen chemical is excited to a higher energy state from its ground state. As the excited molecule returns to the ground state, energy is emitted that is lower in magnitude than the energy initially absorbed. This energy is emitted in the form of longer wavelengths, typically mild heat radiation.

These synthetically derived compounds can be broadly categorized into two groups: UVB (290–320 nm) and UVA (320–400 nm) absorbing chemicals. Sunscreen chemicals are generally aromatic compounds conjugated with a carbonyl group (37). Chemical sunscreens can be classified based on their chemical properties, and each class has its own characteristic absorption spectra (Table 2).

PABA was a widely used sunscreen in the 1950s and 1960s. Several of the properties pertaining to the limitations of PABA can be attributed to its chemical structure: amino and carboxylic acid groups in a *para*-orientation on a benzene nucleus. The highly polar nature of PABA made this agent extremely water soluble, but the increased hydrogen bonding between molecules also promoted a crystalline physical state (39). This led to some difficulty in manufacturing a solvent that ensured continuous dissolution of PABA. The amine and carboxyl groups also made the PABA molecule sensitive to pH changes, and therefore somewhat labile in its effectiveness as a UV chemical absorbing agent. The molecule's lack of stability also led to changes in the color of the product when exposed to air.

Glycerol PABA was subsequently developed to protect the carboxylic acid group from pH changes and therefore was slightly more stable than the original PABA formulation. Other preparations attempted to protect both the carboxyl and the amine

Table 2 Sunscreen Agents and Their UV Protective Wavelengths

Sunscreen	Range of protection (nm)	Maximal effect of protection (nm)
PABA and PABA esters		
PABA	260–313	283
Padimate O	290–315	311
Padimate A	290–315	309
Glycerol aminobenzoate	260–313	297
Cinnamates		
Octyl methoxycinnamate	280–310	311
Cinoxate	270–328	290
Salicylates		
Homosalicylate	290–315	306
Octyl salicylate	260–310	307
Triethanolamine salicylate	269–320	298
Octocrylene	287–323	303
Etocrylene	296–383	303
Benzophenones		
Oxybenzone	270–350	290,325
Dioxybenzone	206–380	284,327
Sulisobenzone	250–380	286–324
Menthylanthranilate	200–380	336
Dibenzoylmethanes		
Tert-butylmethoxydibenzoylmethane (Parsol)	310–400	358
4-isopropyldibenzoylmethane (Eusolex)	310–400	345
Trometrizole trisiloxane, terephthalylidene dicamphor sulfonic acid (Mexoryl XL)	300–400	328

Source: Adapted from Ref. 38.

group. Padimate O (N, N-dimethyl PABA octyl ester), addressed many of the original structure's limitations and became a widely used sunscreen agent. Both the amino and the carboxyl groups are protected, making Padimate O less sensitive to pH changes. This new chemical structure also resulted in decreased intermolecular hydrogen bonding, resulting in a sunscreen agent that is a liquid instead of a crystalline solid.

The original PABA fell out of favor largely because of staining and allergic contact reactions. There is a much higher presence of contact and photocontact allergy to PABA than to other sunscreening agents (40). The PABA derivates also were reported to induce contact sensitization. Sensitization to PABA showed strong reactions to benzocaine, suggesting that reports of glycerol PABA allergy may in fact have been due to impurities in glyceryl PABA preparations (41). Other PABA derivates such as Padimate A, and to a lesser extent, Padimate O, have also been reported to cause sensitization or photocontact sensitization. Padimate A was also found to cause phototoxicity and is no longer used in the United States (42).

Salicylates were the first UV chemical absorbers used in commercially available sunscreen preparations. In contrast to the *para*-distribution of the carboxyl and amine groups, the salicylates are *ortho*-distributed (the carboxyl and amine groups are on neighboring carbon atoms on the benzene ring). This spatial arrangement allows hydrogen bonding within the molecule itself, leading to a UV absorbance of about 300 nm (43). This intramolecular hydrogen bonding results in increased molecule stability, less interaction

with other compounds, and good overall safety record. The salicylate group of sunscreen agents include octyl salicylate and homomenthyl salicylate.

Cinnamates are effective sunscreen agents with a peak absorption wavelength of about 305 nm. They are chemically related to balsam of Peru, coca leaves, cinnamic aldehyde, and cinnamic oil. The chemical structure of the cinnamates, as a group, makes the molecule insoluble to water, requiring more frequent reapplication of the preparation. Contact dermatitis to the cinnamates and cross-sensitization to structurally related products have been reported.

Benzophenone derivates and anthranilates are effective at absorbing UVA radiation. Although the primary protective range for benzophenone is in the UVA range, a secondary protective band is also noted in the UVB range. The most commonly used benzophenone agents are oxybenzone and dioxybenzone. Although these ingredients are much less allergenic than PABA, they do nonetheless still carry a risk of photocontact and contact allergy. Anthranilates, such as menthylanthranilate, provide low-level, yet broad-spectrum coverage. They are commonly added to sunscreens to augment protection. Camphor is an agent widely used in Europe, but not approved for use in the United States. They are effective UVB-absorbing agents.

Dibenzoylmenthanes are a relatively new group of sunscreen agents and are especially effective at offering protection against UVA radiation. Tert-butylmethoxy-dibenzoylmethane (Avobenzone, Parsol 1789) is approved for use in the United States, while isopropyldebenzoylmethane (Eusolex 8020) has been widely used in Europe. The latter has been associated with a high incidence of contact dermatitis, and has not been approved in the United States. In a study of 19 patients with positive photopatch tests to sunscreens, eight showed positive reactions to butyl methoxy dibenzoylmethane (44).

PHYSICAL SUNSCREENS

Physical sunscreens are particles that scatter and reflect UV energy back into the environment. In sufficient quantities, they will serve as a physical barrier to incident UV and visible light. Their popularity has grown in recent years due primarily to their low toxicity profile. These agents are fairly photostable and have not been shown to induce phototoxic or photoallergic reactions. They are also extremely effective in protecting against both UVA and UVB. The most common particulate sunscreen agents are titanium dioxide and zinc oxide.

Early formulations of physical sunscreen agents were not widely accepted because the particulate matters had to be incorporated in high concentrations, resulting in an opaque film on the skin in order to achieve adequate protection. This was often not cosmetically acceptable. Newer formulations which provide "micronized" formulations give rise to a more translucent appearance, and allow for adequate protection with improved cosmetic results. Comparison between zinc oxide and titanium dioxide showed that zinc oxide is superior for UVA protection in the 340–380 nm range and tends to be less pasty on the skin (45).

PHOTOCARCINOGENESIS REDUCTION BY WEARING CLOTHING

Clothing specifically designed to avoid sun exposure should be incorporated into a comprehensive sun-protection program. Transmission of UV radiation through fibers depends on the radiation that is absorbed by the fiber and scattered by the fiber. Polyester

provides more protection than cotton. The cover factor, defined as the ratio of closed spaces to open spaces in the fabric, is the most important factor in determining the photoprotection of the fabric (46). Darker colors provide better protection than lighter colors. To enhance the ultraviolet protection factor (UPF) of clothes, UV-absorbing laundry detergents have been shown to increase the UPF of a cotton T-shirt by 400% (47).

BEHAVIOR MODIFICATION

Sunscreens should be used in conjunction with daily sun-safety behavior in order to achieve maximal photoprotection. Avoidance of UV radiation to the skin is the ultimate goal. Hats, umbrellas, and protective clothing are easy ways to protect the skin. Daily use of sunscreens with frequent reapplication should be a part of the daily routine. Sunbathing and tanning salons should be strictly avoided.

Sun avoidance is easy to advocate, but in reality, difficult to practice. Sunscreen is the most common sun-protection behavior practiced, yet only about 40% of British colleges students admitted to daily sunscreen use (48). Within the adult age range, women and people with sensitive skin were most likely to be using skin protection (49). However, women were also more likely than men to sunbathe deliberately and to use sun-tanning booths. Adolescents have the lowest skin protection rates of all age groups. Less than one-third of U.S. youths, ages 11–18, practice routine sun protection on sunny days during the summer (50). Furthermore, adolescents are increasingly using tanning salons. In a study of 1274 U.S. adolescents, 12% of boys and 42% of girls had tanned indoors (51).

EFFECTIVENESS OF PHOTOPROTECTION

Primary prevention programs for skin cancer that are focused on lowering UV exposure appear to be having a positive effect in lowering skin cancer incidence (52). Persons with a prior history of BCC had fewer subsequent BCCs develop if they protected themselves from UV exposure (53).

Reduction in sun exposure by daily use of a sunscreen may reduce risk of SCC (54). A meta-analysis of 11 studies of melanoma risk and sunscreen usage showed only a small protective advantage (55). However, when evaluating only the more recent studies where high-SPF sunscreens were available, there appeared to be a protective effect and other inherent flaws associated with retrospective studies which may be responsible for protection not being noted (Table 3) (70).

PHOTOPROTECTION AND VITAMIN D

Sunlight is important in the generation of Vitamin D in the skin. In addition to eating foods containing vitamin D, an essential hormone for normal bone development, sunlight exposure also plays a critical role in supplying the human body with its necessary dose of vitamin D (71). Sunlight converts cutaneous stores of 7-dehydrocholesterol (provitamin D3) to previtamin D3 (precholecalciferol) and then to vitamin D3 (cholecalciferol). Vitamin D3 is also the form obtained though ingestion of foods. Once in the body, vitamin D3 is hydroxylated first in the liver to 25-hydroxyvitamin D (25-OHD), and then subsequently hydroxylated again to the active form, 1,25-dihydroxdyvitamin D [1,25-(OH)2D], by the kidneys. It should be noted that 25-OHD is a measure of body stores of Vitamin D.

Table 3 Studies Evaluating Protective Effects of Sunscreens on Melanoma

Study	Interval of sunscreen use examined	Findings
Klepp 1979 (56)	1974–75	Increased MM in users
Graham 1985 (57)	1974–80	NS
Herzfeld 1993 (58)	1977–79	NS
Beitner 1990 (59)	1978–83	Increased MM in a subset of users
Green 1986 (60)	1979–80	Protective for MM
Holman 1986 (61)	1980–82	NS
Osterlind 1988 (62)	1981–85	NS
Holly 1995 (63)	1981–86	Protective for MM
Westerdahl 1995 (64)	1988–90	Increased MM in users
Rodenas 1996 (65)	1989–93	Protective for MM
Autier 1995 (66)	1991–92	Increased MM in users
Espinosa 1999 (67)	1994–97	Protective for MM
Naldi 2000 (68)	1994–98	NS
Westerdahl 2000 (69)	1995–97	Increased MM in a subset of users

Abbreviation: NS, not significant.

Because sunlight is considered to be the most important source of vitamin D, there has been concern that photoprotection may, in fact, be contributing to its deficiency. Vitamin D deficiency increases the risk of bone disease, muscle weakness, and possibly certain types of cancer (72,73). In one study, the application of a sunscreen was shown to reduce the skin's ability to synthesize vitamin D3 (74). 25-hydroxy vitamin D levels have also been shown to be reduced with chronic sunscreen use (75). The active form of vitamin D, 1,25-dihydroxyvitamin D, was shown to be lower in patients using sunscreen compared to a placebo group who did not use sunscreen (76). Although values were lower for the sunscreen group, they still remained within the normal range. However, other studies have reported conflicting findings (77).

Studies of individuals who consistently sustain a lifestyle involving photoprotection have failed to show clinical evidence of vitamin D deficiency. A study of eight xeroderma pigmentosum patients showed that, although 25-OHD levels were low normal, the 1,25(OH)2D levels were normal (78). The lack of seasonal variation in 25-OHD levels showed that the patients received the same amount sunlight (or lack thereof) throughout the year. The evidence provided in this study is supported by epidemiologic studies of sunscreen use, which failed to show that regular sunscreen use led to vitamin D deficiency (79).

Recent media attention to the issue of vitamin D and sunlight reinforces the need for patient education. Although sunlight exposure is important as a source of vitamin D, photoprotection does not result in vitamin D deficiency. Furthermore, the use of tanning beds should not be used as a source of vitamin D. Patients concerned about their vitamin D levels should be encouraged to eat foods rich in vitamin D, such as fish liver oils, egg yolks, and milk fortified with vitamin D or take oral vitamin D supplements.

PATIENT RECOMMENDATIONS AND FUTURE DIRECTIONS

There appears to be a direct relationship between UV exposure and the development of photocarcinogenesis. Based upon the best current information available, a regimen of overall photoprotection which includes protective clothing, avoiding midday sun, and

regular use of broad-spectrum high SPF sunscreen should provide significant protection and appears to be reducing melanoma incidence rates. This is the current recommendation of the American Academy of Dermatology, Skin Cancer Foundation, and other major international organizations, and it is also the recommendation that is best supported by the existing data. There is no reason to recommend intentional sun exposure or decreased photoprotection to increase vitamin D levels as adequate incidental UV exposure occurs in day-to-day activities. Hopefully, we will have even more definitive answers to questions related to the optimization of effectiveness of sunscreens and other forms of photoprotection and for reducing the risk from exposure to UV radiation as improved photoprotective agents, strategies, and methods are developed in the future.

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