

Invited Review

A Review of Sunscreen Safety and Efficacy

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ABSTRACT

The use of sunscreen products has been advocated by many health care practitioners as a means to reduce skin damage produced by ultraviolet radiation (UVR) from sunlight. There is a need to better understand the efficacy and safety of sunscreen products given this ongoing campaign encouraging their use. The approach used to establish sunscreen efficacy, sun protection factor (SPF), is a useful assessment of primarily UVB (290–320 nm) filters. The SPF test, however, does not adequately assess the complete photoprotective profile of sunscreens specifically against long wavelength UVAI (340–400 nm). Moreover, to date, there is no singular, agreed upon method for evaluating UVA efficacy despite the immediate and seemingly urgent consumer need to develop sunscreen products that provide broad-spectrum UVB and UVA photoprotection. With regard to the safety of UVB and UVA filters, the current list of commonly used organic and inorganic sunscreens has favorable toxicological profiles based on acute, subchronic and chronic animal or human studies. Further, in most studies, sunscreens have been shown to prevent the damaging effects of UVR exposure. Thus, based on this review of currently available data, it is concluded that sunscreen ingredients or products do not pose a human health concern. Further, the regular use of appropriate broad-spectrum sunscreen products could have a significant and favorable impact on public health as part of an overall strategy to reduce UVR exposure.

INTRODUCTION

The incidence of nonmelanoma and melanoma skin cancers has been increasing in most parts of the world for several

decades (1,2). Exposure to UV radiation (UVR)[†] from the sun plays a causal role in acute and chronic skin damage including skin cancers (3). As such, the medical community and other health care providers have advocated a photo-avoidance strategy consisting of limiting sunlight exposure between midday hours of 1100 and 1500, wearing protective clothing and using sunscreens. Because sunscreens prevent sunburn and their use is encouraged, it has been suggested that sun exposure may actually be prolonged because users believe they are protected and therefore will spend more time in the sun. This potential consequence raises several ancillary concerns. For example, because most sunscreens are primarily UVB (290–320 nm) and, in some cases, short wavelength UVAII (320–340 nm) filters, then use of such products changes the UVR spectrum to which the skin is exposed. Consequently, if behavior is modified by sunscreen use resulting in longer periods of sun exposure, then the dose of long-wavelength UVR, 340 nm and above, would be increased. Further, even though sunscreens prevent sunburn, little is known regarding the threshold or dose-response for UVR-induced effects on other endpoints such as immunosuppression or DNA damage. Finally, because sunscreens are becoming widespread and available, questions have been raised regarding their long-term safety, particularly in the presence of UVR. The intent of this review is to address these concerns, when possible, with direct evidence and discuss ways that sunscreen products might be improved. To this end, it seems necessary to examine some basic concepts regarding the complexities of UVR and its effects on skin. After considering the effects of UVR on unprotected skin, the consequences of introducing sunscreens into this intricate interaction will be reviewed.

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[†]Abbreviations: BAS, 3-benzoyl-4-hydroxy-6-methoxybenzenesulfonic acid; CHO, Chinese hamster ovary; CW, critical wavelength; EMR, electromagnetic radiation; MED, minimal erythema dose; 8-MOP, 8-methoxypsoralen; NMSC, nonmelanoma skin cancer; OMC, octyl methoxycinnamate; OTC, over-the-counter; PABA, *p*-aminobenzoic acid; SPF, sun protection factor; SPS, sunscreen protected spectrum; SSR, solar-simulated radiation; TiO₂, titanium dioxide; UVAI, 340–400 nm radiation; UVAII, 320–340 nm radiation; UVB, 290–320 nm radiation; UVC, 100–290 nm radiation; UVR, ultraviolet radiation; ZnO, zinc oxide.

SOLAR UVR

The sun emits non-ionizing electromagnetic radiation (EMR) composed of UV (100–400 nm), visible (400–780 nm) and infrared (780–5000 nm) radiation. With regard to human health, the most relevant and concerning form of EMR is UVR (4–6). Ultraviolet radiation is composed of wavelengths between 100 and 400 nm that are further divided into UVC (100–290 nm), UVB (290–320 nm) and UVA (320–400 nm). Because wavelengths below 290 nm are absorbed by atmospheric ozone and do not reach the earth's surface, UVC from sunlight is of little practical concern (7).

As stated, the primary source of UVB and UVA radiation is the sun, to which exposure is considered largely unavoidable. The amount of UVR reaching a given location on earth varies seasonally, geographically and diurnally. For example, UVR intensity is highest at the equator and high altitudes and decreases with increasing latitudes. The intensity of UVB is considered highest during the summer months and on a daily basis between 1100 and 1500 h. Importantly, however, UVA intensity is more consistent throughout the day and from season to season compared to UVB. Meteorological and atmospheric conditions including cloud cover, pollution, humidity and temperature modify the spectrum and intensity of terrestrial sunlight, particularly the UV component (8). For most individuals in developed countries, exposure to solar UVR comes in short, multiple episodes to the face, neck and hands (9) that are a consequence of everyday life. This incidental exposure can account for as much as 80–90% of an estimated yearly exposure to UVR (10,11) and, not coincidentally, over 60% of nonmelanoma skin cancers (NMSC) appear at these sites (3,12,13).

EFFECTS OF SOLAR UVR ON THE SKIN

Exposure to UVR has pronounced acute, chronic or delayed effects on the skin. The UVR-induced skin effects manifest as acute responses such as inflammation, *i.e.* sunburn (14), pigmentation (15), hyperplasia (16), immunosuppression (17,18) and vitamin D synthesis (19,20), and chronic effects, primarily photocarcinogenesis (3,21) and photoaging (22–24). These acute and chronic effects are dependent on the spectrum and cumulative dose of UVR; however, the complete action spectrum for the majority of UVR-induced effects has not been completely defined in human skin. In addition, and quite importantly, these responses have different thresholds such that the prevention of UVR-induced changes for one endpoint does not guarantee a similar level of protection for any other. Regardless, it should be kept in mind that exposure to UVR always produces more skin damage in unprotected than in sunscreen-protected skin because the acute and chronic effects of UVR are dose, time and wavelength dependent (3), and in the most empirical terms sunscreens reduce the dose of UVR.

Evidence for a role of UVR in skin cancers

Exposure to UVR from sunlight probably causes NMSC, based in part on the following evidence:

- People with xeroderma pigmentosum, a genetic disease with defective DNA repair, are exquisitely sensitive to UVR

and develop NMSC at an early age predominantly on sun-exposed parts of the body (25).

- The incidence of NMSC is inversely related to latitude in populations of mainly European origin (26) and is greater in outdoor compared to indoor workers (27).

- The NMSC is most common on the head, neck, arms and hands, areas of the body that receive the largest dose of UVR (28).

- Persons that easily sunburn, *i.e.* Fitzpatrick skin types I and II, are more susceptible to the development of NMSC (29,30).

- Mutations in the p53 tumor suppressor gene have been found in 90% of squamous and 50% of basal cell carcinomas, most of which are UVR signature mutations (31,32).

- Exposure to UVR produces dose-, time- and wavelength-dependent skin tumors in animals (3,21).

The case for the role of sunlight exposure as a risk factor for development of malignant melanoma is more complex compared to NMSC. Nonetheless, there is epidemiological evidence supportive of the role of sunlight exposure, particularly severe sunburn in childhood, as a risk factor for melanoma (2,33). Sun sensitivity, that is pigmentation traits such as color of eyes, hair and skin, and skin reaction to sun exposure, *i.e.* inability to tan, and intermittent exposure to intense sunlight are important determinants of susceptibility to melanoma (34,35). Interestingly, in contrast to NMSC, UVB-mediated p53 mutations are virtually absent in melanomas (31), which suggests separate mechanisms responsible for the development of these skin cancers.

Evidence for a role of UVR in photoaging

Like skin cancer, chronic exposure to solar UVR is thought to accelerate aging of human skin. This skin photoaging is characterized by dryness, roughness, irregular pigmentation such as freckling/lentigenes, actinic keratoses, wrinkling, elastosis, inelasticity and sebaceous hyperplasia (24). The incidence and severity of skin photoaging are believed to be a function of cumulative UVR exposure, based on human and animal studies. For example, Caucasian women with excessive sun exposure have a higher incidence of photoaging than women with a low UVR exposure history (36,37). In addition, signs of photodamage specifically on the face are absent in unexposed skin, *e.g.* inner portion of the arm, of the same individual (38). Importantly, photoaging differs from chronological or intrinsic aging of the skin and may be slowed or reversed by reduction in UVR exposure as is the case with sunscreens or, perhaps, with other treatments such as all-*trans*-retinoic acid (39).

SUNSCREENS AS PART OF A PHOTOPROTECTION STRATEGY

Sunscreen-mediated photoprotection is concerned with the reduction of exposure to UVR, specifically UVB and UVA, primarily from the sun. There are two categories of sunscreen agents: organic and inorganic. The organic sunscreens are referred to as soluble or chemical sunscreens. The inorganic sunscreens are commonly known as physical, mineral, insoluble, natural or nonchemical. The term nonchemical is an obvious misnomer that has gained some consumer

Table 1. List of UVR filters used in the United States skin care market

UV filter (approximate rank order)	Comment
Octyl methoxycinnamate (OMC)	Found in over 90% of sunscreen products used in the world
Oxybenzone	Combined with OMC in many beach products
Octyl salicylate	Used in oxybenzone/OMC primarily for its solvent properties
Octocrylene	Found in many recreational sunscreen products
2-Phenyl-benzimidazole-5-sulfonic acid (PBSA)	Used in combination with OMC in daily UV protectant products
Methyl anthranilate	
Homosalate	
2-Ethylhexyl-o-dimethylamino	
Benzoate (Padimate O)	
Avobenzone	Currently four products
Zinc oxide	Recently approved category I sunscreen
Titanium dioxide	
<i>p</i> -Aminobenzoic acid (PABA)	Rarely used
Glyceryl aminobenzoate	Rarely used
Amyl <i>p</i> -dimethylamino-benzoate (Padimate A)	Rarely used
Ethyl 4 [bis(hydroxypropyl)] amino	Rarely used
Dioxybenzone	Rarely used
Sulidobenzene	Rarely used
Cinoxate	Rarely used
Diethanolamine <i>p</i> -methoxycinnamate	Rarely used
Lawson + dihydroxyacetone (DHA)	Rarely used
Red petrolatum	Rarely used
Sodium 3, 4-dimethyl-phenyl glyoxylate	Rarely used
Benzoate digalloyl trioleate	Rarely used
Tiethanolamine salicylate	Rarely used

recognition nonetheless. The distinction between these two categories of sunscreens is somewhat arbitrary based on mechanism; however, for the purpose of this review, we will use this distinction and address each separately.

Organic sunscreens

Organic sunscreens have been the mainstay of sunscreen formulation for decades and, although inorganic sunscreens are gaining in popularity, organic sunscreens are still used in greater amounts. Organic sunscreens are often classified as derivatives of: (1) anthranilates, (2) benzophenones, (3) camphors, (4) cinnamates, (5) dibenzoylmethanes, (6) *p*-aminobenzoates or (7) salicylates (40). These aromatic compounds absorb a specific portion of the UVR spectrum that is generally re-emitted at a less energetic, longer wavelength, *i.e.* heat or light, or used in a photochemical reaction, such as *cis-trans* or keto-enol photochemical isomerization (40).

There are 23 (including red petrolatum) organic sunscreen agents currently available in the United States for use in over-the-counter (OTC) sunscreen products (Table 1). Of

these, nine are ordinarily used in sunscreen products and the remaining are rarely if ever present in sunscreen products marketed today. Of the nine sunscreens that are used, five of these comprise the majority of sunscreen products used in the world. The organic sunscreens are almost always used in combination because no single organic sunscreen agent, used at levels currently allowed by the U.S. Food and Drug Administration (41), can provide a high sun protection factor (SPF). Further, individual organic sunscreens have a relatively narrow absorption spectrum that can be broadened by combinations. Specific combinations of organic sunscreens are used frequently depending on the intended product usage, recreational or daily photoprotection and the desired attributes such as waterproof or sweat-proof. Most recently, the combination of organic and inorganic sunscreens has become increasingly popular in sunscreen products.

Inorganic sunscreens

During this decade, the inorganic sunscreens have been used with increasing frequency in beach and daily use photoprotection products. This has been driven, in part, by their safety and effectiveness, particularly in blocking UVA, and the concern regarding potential adverse effects of organic sunscreens. The inorganic sunscreens are generally viewed as harmless pigments that cannot enter the skin and are largely unaffected by light energy like organic sunscreens may be. The two most commonly used inorganic sunscreens are titanium dioxide (TiO₂) and zinc oxide (ZnO). Although these two metal oxides differ substantially in their appearance and attenuation spectra (42), they share some general properties that are discussed briefly.

Zinc oxide and TiO₂ exist as odorless white powders comprised of a Gaussian or normal distribution of particle sizes. Microfine powders, used in sunscreen products, have an average particle size of approximately 0.20 μm (micron) or less with a distribution that is narrow and well controlled. Importantly, compared to the traditional pigment grades of these metal oxides that have been used for years in cosmetic products, microfine powders do not contain smaller particles, rather the lower end of the normal particle size distribution is augmented through specialized manufacturing procedures. In other words, microfine powders have always been present in ZnO- or TiO₂-containing products but were optically overwhelmed by the larger particles. Thus, microfine particles do not represent an entirely new particle size, just a refinement of the existing particle size distribution (43).

Each particulate has a size at which it maximally scatters visible light (43). This is the ideal size for use as a white or colored pigment. As a sunscreen, however, any color rendered to the product by an ingredient is undesirable. Thus, the average particle size of a metal oxide is reduced below the optimal light scattering size, allowing visible light to be transmitted and therefore, appearing virtually invisible on the skin. This property has been employed to yield the microfine grades of metal oxides that are now being widely used in sunscreen and daily skin care formulations.

Zinc oxide or TiO₂ used in sunscreen preparations is often coated with other materials such as silicones, fatty acids or oxides of aluminum, silicon or zirconium to aid in dispersion. The coatings were developed by the paint industry to

reduce particle agglomeration, which improves the distribution of particles when applied as a thin film on a surface. The proper coating provides better compatibility between the particle and the dispersion medium, which ultimately improves aesthetics and decreases processing costs. Further, coating may reduce any potential photoreactivity of the metal oxides (44).

SUNSCREEN EFFICACY

Sunscreens represent unique products because, if applied properly, their efficacy is guaranteed. This guarantee is based on their ability to prevent sunburn, which has been the criterion used to evaluate these products to date. As presented in this paper, however, this singular criterion does not appear to be sufficient for evaluation of sunscreen products in the future. This view is based on the need for broad-spectrum UVB and UVA photoprotection products. Nonetheless, unlike any other OTC drug, the final sunscreen product is tested for efficacy before consumer distribution. The methods used to evaluate the efficacy of sunscreens will be briefly considered.

SPF: A measure of protection against UVB

There is no question regarding product efficacy—sunscreens prevent sunburn. The selection of a sunscreen or combination of sunscreens and the resultant formulation is designed and evaluated for this purpose. The SPF for a sunscreen is defined as the ratio of sun exposure that skin can tolerate before burning or minimal erythema is apparent with and without sunscreen protection. Thus, SPF is really the protection factor for sunburn.

Because the action spectrum for UVR-induced sunburn is similar to that for a specific measure of DNA damage, it often has been inferred that protection against sunburn is the same as protection against DNA damage and a host of other endpoints as well. However, as mentioned previously, it is now clear that each biological response has a unique action spectrum and even when different responses have similar action spectra the threshold or dose-response or both to UVR may differ dramatically (3,14,17,19–23,39). Thus, although SPF provides a measure of sunburn protection, its value for other endpoints is limited and could be viewed as misleading.

Measures of UVA efficacy

When the SPF system originated, it was commonly accepted that the action spectrum for UVR-related skin changes or damage was similar to that for erythema in human skin. For example, the action spectrum for NMSC in rodents is similar to that for erythema in human skin (21). Of course, we now know that the action spectra for other endpoints such as photoaging and, perhaps melanoma, are not the same as erythema. Because SPF utilizes erythema as the endpoint, and UVA is only mildly erythrogenic, it seems obvious that SPF alone does not adequately describe a sunscreen's protective profile. In pragmatic terms, it is possible to have an SPF 15 sunscreen that blocks only a limited amount of UVB (320–340 nm) and virtually no UVA (340–400 nm). Remarkably, this describes the majority of sunscreen products on the market in the United States today.

The ideal test for UVA photoprotection should use, as an endpoint, some biological event known to be mediated by these wavelengths. Unfortunately, to date, an endpoint for use as a representative surrogate for UVA events has not been agreed upon. There are several *in vivo* tests that have been proposed but not widely adopted. For example, immediate pigment darkening (45), 8-methoxypsoralen (8-MOP) phototoxic protection (46) and UVA erythema protection (47) have been studied to varying extents, each with some critical concern, such as exaggerated protection factors in 8-MOP-sensitized skin (46) or lack of UV-dose reciprocity for UVA-induced erythema (45).

Similarly, *in vitro* tests have been described, most of these based on some manipulation of spectrophotometric measurements. One of these, the critical wavelength (CW), has been proposed to evaluate sunscreens for their UVA absorption, based on the methods outlined by Diffey (48). In this method, the transmission through a substrate, both with and without the sunscreen, is measured on a wavelength-by-wavelength basis using a light source with a continuous output over the terrestrial UVR spectrum. The attenuation spectrum of the sunscreen is then determined. Importantly, prior to attenuation testing, the sunscreen can be subjected to a preirradiation step, thus testing for any photoinstability of the product. The CW is the wavelength at which 90% of the total area under the attenuation spectrum from 290 to 400 nm is obtained. This procedure provides a qualitative means by which the UVA attenuation of a sunscreen product may be assessed.

Considering the current need for broad-spectrum UVB/UVA sunscreen products and the absence of a meaningful and clinically viable biologic marker, it would seem best to document, at a minimum, that the sunscreen attenuates radiation of the proper spectrum. To this end, proponents of the CW method stress its simplicity, reproducibility and its ability to account for product photoinstability. Nonetheless, critics suggest that the human relevance is uncertain because it is an *in vitro* test where no biological endpoint is measured.

SUNSCREEN SAFETY

Besides traditional recreational and daily photoprotection products, sunscreens are increasingly included in diverse consumer products. Given this, questions regarding their long-term safety, particularly in the presence of UVR exposure, have been raised. The intent of this section, therefore, is to address some current concerns regarding sunscreen safety. This is not a comprehensive review of the published studies on sunscreen safety, rather an attempt to compare and contrast results of *in vitro* studies with those obtained *in vivo*.

It is important to distinguish between long-term safety concerns and short-term adverse reactions. Sensitivities, both photo- and nonphotoinduced, to organic sunscreens are well documented and seemingly rare events, although there are few published studies making it difficult to know the actual prevalence (49–51). These important and meaningful events likely impact compliance but do not represent the sort of long-term toxicity issues we discuss in this paper.

In general terms, the toxicological evaluation of any

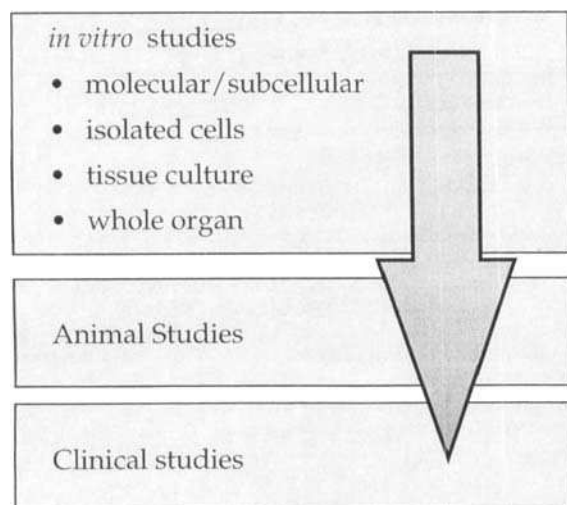


Figure 1. Toxicological hierarchy in assessment of human risk. This cartoon represents different levels of human relevance from a toxicological viewpoint. Results from *in vitro* studies need to be balanced against animal and clinical studies when considering risk to human health.

chemical where human exposure is likely often includes short-term *in vitro* studies that are believed to be predictive of long-term or delayed toxicity. This is quite evident in the carcinogenic risk assessment of chemicals where bacteria mutation assays have become a mainstay in this process. With regard to sunscreens, assessment of the mutagenic potential represents a unique challenge considering their specific function, namely absorption of UVR. As such, short-term *in vitro* approaches measuring various endpoints have been conducted with sunscreens, many of which include UVR exposure. In general, these are cytotoxicity or genotoxicity, *i.e.* bacteria mutagenicity and mammalian cell clastogenicity studies that include concurrent UVR exposure. The photogenotoxicity testing of a chemical is judged against results obtained with a positive control, 8-MOP. Because 8-MOP is the only demonstrated human photocarcinogen known, the assessment of any compound using these *in vitro* tests is tenuous at best. Nonetheless, there are a number of studies examining the acute interaction between UVR and chemicals for both organic and physical sunscreens. In general, these studies have been conducted to identify what effects sunscreens have on UVR-induced damage, either genetic or cytotoxic, and, by inference, UVR-induced skin carcinogenesis. This strategy remains in the infant stages of development, although to date, this approach appears to have little bearing on human safety assessment.

Finally, when evaluating the human safety of sunscreens and other xenobiotics, it is important to understand the hierarchical value of the experimental results. For example, studies conducted in humans provide direct evidence in the species of interest thereby eliminating issues regarding extrapolation and relevance inherent in animal and *in vitro* investigations. Similarly, studies conducted in animals provide an integrated response resembling the human circumstance more closely than *in vitro* single cell studies. This hierarchical prioritization, crudely illustrated in Fig. 1, is critical

when considering the potential human health risk from exposure to a chemical.

Studies with organic sunscreens

p-Aminobenzoic acid (PABA) was patented in 1943 and for many years was the primary organic sunscreen active used. Derivatives of PABA including 2-ethylhexyl-*o*-dimethylaminobenzoate (Padimate O) and amyl *p*-dimethylaminobenzoate (Padimate A) were developed and utilized during the 1960s and 1970s. Since then a number of other sunscreen agents have become available, several with reduced probability of photorelated toxicity making PABA and its derivatives rarely used sunscreens. Despite its infrequent use, PABA has been the subject of much research.

In vitro photochemistry and cytotoxicity studies. Hodges *et al.* (52) was among the first to show that bacterial cytotoxicity to PABA was enhanced after UVR exposure. Subsequently, it was found that PABA can sensitize the formation of cyclobutane dimers in DNA of bacterial and mammalian cells (53). Following these studies, PABA was shown to form adducts with thymine and thymidine after UV irradiation (54,55). The consequences of PABA photosensitization of thymine dimers and direct adducts was extended to aqueous solutions containing bacterial plasmid DNA with a similar result (56). These authors suggested that PABA and two other sunscreens, benzophenone-9 and 2-phenylbenzimidazole-5-sulfonic acid, were potential carcinogens based on these *in vitro* data. Along these same lines, Knowland *et al.* (57) reported that the 2-ethylhexyl-*o*-dimethylamino derivative of PABA, Padimate O, was harmless in the dark but mutagenic following exposure to sunlight or, more correctly, solar-simulated radiation (SSR) from an artificial light source. This work conducted in yeast was extended by McHugh and Knowland (58), where it was reported that irradiated Padimate O generates DNA strand breaks and lesions that are blocked by free radical scavengers, likely related to the formation of singlet oxygen following irradiation (59). Collectively, these data suggest that PABA-like sunscreens might represent a human hazard if applied and exposed to UVR from sunlight as intended.

In vitro photogenotoxicity studies. Although some of the studies discussed above could be viewed as evidence for photogenotoxicity, it has not been until recently that the classical bacterial mutagenicity, *i.e.* Ames test, and mammalian cell clastogenicity studies have been modified to include UVR as a means to evaluate sunscreens. These photogenotoxicity studies have given somewhat mixed results for sunscreens and clearly more work is needed to validate these methods. Regardless, Dean *et al.* (60) reported that PABA was photoclastogenic but not photomutagenic using Chinese hamster ovary (CHO) cells or *Escherichia coli* bacteria, respectively. The lack of photomutagenicity of PABA was confirmed by Chételat *et al.* (61) and Henderson *et al.* (62). However, in contrast to Dean *et al.* (60), Chételat *et al.* (63) found that irradiated PABA was not clastogenic in CHO cells under the conditions of their study. In another study, Mondon and Shahn (64) found that PABA actually protected against lethal and genotoxic effects of UVB in V79 Chinese hamster cells and yeast. Finally, UV-induced unscheduled DNA synthesis was found to be blocked by PABA

in cultures of human keratinocytes or fibroblasts (65,66). Therefore, at a minimum, these data cast doubt on the potential human concern related to the use of products containing organic sunscreens.

Acute in vivo studies. From the *in vitro* study results above, it is apparent that under specific artificial conditions, organic sunscreens, predominantly PABA and its derivatives, can interact with DNA following UVR either directly or indirectly. The effect of PABA and other organic sunscreens on measures of DNA damage produced by acute exposure to UVR has been evaluated *in vivo* using primarily hairless mice. Walter (67) and Walter and DeQuoy (68) found that several organic sunscreens including PABA and its derivatives reduced UV-induced DNA damage in the skin of hairless mice. More recently, Ley and Fourtanier (69) reported that octyl methoxycinnamate (OMC), the most common UVB sunscreen used in the world, and terephthalylidene dicamphor sulfonic acid, a UVB/UVA filter, reduced the number of UV-induced pyrimidine dimers in epidermal DNA of hairless mice exposed to SSR.

Most recently, studies investigating UVR-induced mutations in the p53 tumor suppressor gene have been conducted. As stated earlier, it has been reported that the p53 tumor suppressor gene is mutated in 90% of squamous cell carcinomas and 50% of basal cell carcinomas from human subjects (31). Ananthaswamy *et al.* (70) described the ability of sunscreens, one containing the UVB filters octocrylene and 2-phenylbenzimidazole-5-sulfonic acid and the other containing the same UVB filters plus UVA filters avobenzone and terephthalylidene dicamphor sulfonic acid, to inhibit the induction of p53 mutations in UVR-irradiated C3H mouse skin. In order to avoid the tedious task of examining all 11 exons of p53, these authors selected a site that is mutated in 27% of UV-induced skin tumors in mice for sequence analysis. They showed that the application of sunscreens before each irradiation nearly abolished the occurrence of p53 mutations at the selected site. In these studies artificial light emitting only a portion of the solar spectrum was employed, which means that these mice were not exposed to the high doses of longer wavelength UVA and shorter wavelength visible light that is contained in the solar spectrum. Nonetheless, this is an important study because it examined the effects of sunscreens on a molecule that influences the fate of a cell.

Chronic in vivo studies. In considering the causal, quantitative relationship between UVR and skin cancer as suggested by Blum *et al.* (71), it struck many that reducing UVR exposure would not only support this relationship but may be a practical means of reducing skin cancers in humans. Studies using rodents, predominantly hairless mice, have established a cause and effect relationship between UVR exposure and NMSC. An action spectrum for UVR-induced skin cancer in hairless mice has been reported and continues to be refined (21). Thus, it is not surprising that animal studies have been conducted examining the ability of sunscreens to prevent UVR-induced skin cancer. To this end, there are at least 21 published studies conducted since 1960 that have found without exception that UVR-induced skin tumor formation in rodents is inhibited by topical treatment with individual or combinations of sunscreens. A list of these studies is presented in Table 2.

Table 2. Summary of photo co-carcinogenicity studies with sunscreens

Test materials	References
Single compounds	
Titanium dioxide	Greenoak <i>et al.</i> (97), Bestak and Halliday (98)
Octyl methoxycinnamate (OMC)	Gallagher <i>et al.</i> (141), Reeve <i>et al.</i> (142), Forbes <i>et al.</i> (82), Reeve <i>et al.</i> (80), Fourtanier <i>et al.</i> (143), Bestak and Halliday (98), Reeve and Kerr (79), Kligman <i>et al.</i> (83)
<i>p</i> -Aminobenzoic acid (PABA)	Snyder and May (73), Flindt-Hansen <i>et al.</i> (74-76)
Octyl dimethyl PABA (Padimate O)	Kligman <i>et al.</i> (77), Reeve <i>et al.</i> (80), Bissett <i>et al.</i> (144), Reeve and Kerr (79), Bissett and McBride (145)
Glyceride PABA	Wulf <i>et al.</i> (81)
Mexoryl SX	Fourtanier (143)
3-Benzoyl-4-hydroxy-6-methoxy benzenesulfonic acid (BSA)	Knox <i>et al.</i> (72)
Combinations	
Oxybenzone + OMC	Wulf <i>et al.</i> (81), Kligman <i>et al.</i> (83)
Oxybenzone + Padimate O	Kligman <i>et al.</i> (77)
OMC + 1,7,7 trimethyl-3-benzylidene-bicyclo-[2.2.1]-2-heptone	Young <i>et al.</i> (146)
OMC + avobenzone	Bissett <i>et al.</i> (23), Young <i>et al.</i> (147)
OMC + oxybenzone + avobenzone	Kligman <i>et al.</i> (83)

One of the first published studies examining the ability of sunscreens to inhibit UVR-induced skin cancer in rodents was the work of Knox *et al.* (72). They conducted a series of experiments with mice to determine the effect of a benzophenone derivative, 3-benzoyl-4-hydroxy-6-methoxybenzenesulfonic acid (BAS), or PABA on the development of skin cancer produced by artificial UVR. Both BAS and PABA were found to decrease UVR-induced tumor formation. Consistent with these results are the studies by Snyder and May (73) and Flindt-Hansen *et al.* (74,75) that found topical treatment with PABA significantly reduced the tumorigenic effects of UVR in mice. Furthermore, Flindt-Hansen *et al.* (76) demonstrated that preirradiated, photodegraded solutions of PABA still protected mice against UVR-induced tumor formation. Thus, in contrast to *in vitro* results demonstrating enhancement of UVR dimer formation or photomutations that lead to the logical hypothesis that PABA would enhance UV-induced tumorigenesis, these *in vivo* data convincingly demonstrate that this sunscreen protects against UVR-induced tumor formation in mice.

Studies with PABA derivatives have, in general, been shown to protect against UV-induced skin tumor formation in rodents. For example, Kligman *et al.* (77) found that Padimate O, the alleged photomutagen (55,78), significantly reduced UVR-induced tumor formation in albino hairless mice. More recently Reeve and Kerr (79) found that a solution of Padimate O with a protection factor of 6, nearly abolished the tumor response even at UV doses equal to the protection factor, *i.e.* six times the minimal dose to produce edema in the hairless mouse. Interestingly, an earlier report

by this same group, Reeve *et al.* (80), failed to demonstrate a protective effect of Padimate O in mice pretreated with the carcinogen, 7,12-dimethylbenz(a)anthracene and exposed to chronic UVR, suggesting perhaps that Padimate O might be more effective against UVR initiation compared to promotion. Finally, Wulf *et al.* (81) reported that a glyceride-PABA-containing sunscreen delayed UV-induced tumorigenesis in hairless mice. Collectively, these studies are consistent with those using PABA that find sunscreens protect against UV-induced skin tumor formation in rodents. Most important, these *in vivo* data clearly oppose the *in vitro* results.

Additional studies with other sunscreens and sunscreen combinations have been conducted and are presented in Table 2. Despite the exaggerated UVR exposure resulting in tumorigenesis in most animals in these studies, treatment with sunscreens alone or in combination significantly delayed or completely abolished UVR-induced tumor formation. In addition, several key points emerge from these data that warrant comment. For example, treatment with sunscreens reduces UVR-induced tumor formation in a dose-dependent manner (82) and inhibits UVR-induced tumor initiation (82) and UVR-induced tumor promotion following initiation with either a potent chemical carcinogen (73,80) or UVR itself (75). In several studies where sunscreens reduced UVR-induced tumor formation, there were skin responses observed even in the presence of sunscreen indicative of a significant UVR exposure (72,77), and in at least two studies (80,83) exposure to UVR was increased to the SPF of the product resulting in substantial, repeated UV exposure. In addition, even preirradiated photodegraded PABA blocked completely UVR-induced tumor formation in hairless mice (76). Finally, considering the epidermal permeability of hairless mouse skin together with the duration and frequency of treatment, it is reasonable to suggest that these conditions maximize the concentration of sunscreen products, *i.e.* parent compound, metabolites and any potential photodegradation products, in the skin over time and therefore assess the toxicological potential of any photodegradation products in these studies. Thus, *in toto*, these data would seem to diminish if not eliminate concerns from *in vitro* photocytotoxicity or photomutagenicity studies with respect to long-term sunscreen toxicity, specifically photocarcinogenicity concerns.

Studies with inorganic sunscreens

Although metal oxides, TiO_2 and ZnO , have been used for years in consumer products and are generally considered to be inert, recent photocatalytic applications of TiO_2 (84,85) have led some to a reconsideration of their effect in sunscreens. TiO_2 is a semiconductor that can absorb light and under certain conditions generate free radicals (43,44,78). The band gap (3 eV for TiO_2) is a measure of the minimum energy in electron volts required to promote an electron from the valence band to the conduction band. A compound with a band gap in the region of 3 eV can be excited by radiation at wavelengths below ~ 380 nm. Thus, TiO_2 may be susceptible to excitation by UVB and UVA in sunlight. Photoexcitation of TiO_2 could promote a single electron from the valence band to the conduction band, leaving a positively

charged space, or hole, behind. Usually, the electron recombines with the hole, but sometimes the hole migrates to the surface of the particle, where it can react with absorbed species. In an aqueous environment it can react with water or hydroxyl ions, forming hydroxyl radicals (86). Such processes are well known for aqueous preparations of TiO_2 exposed to either artificial UV light or natural sunlight. In this capacity, the photocatalytic potential of TiO_2 has been used experimentally to degrade suspensions of organic materials and purify drinking water (87).

Considering the photocatalytic potential of metal oxides, it has been proposed as well that a photoreactive pigment in a sunscreen product may degrade organic UVR filters also present in the formula. This has been studied using commercially representative sunscreens that contained both organic and inorganic sunscreens (88). Thin films of the sunscreens were applied to a synthetic substrate and irradiated with increasing doses of solar-simulated UVR, the highest dose being 30 J/cm^2 . The sunscreen and substrate were digested and the percent organic sunscreen remaining was determined. Both coated, microfine ZnO and TiO_2 were shown to be photoprotective with respect to the organic sunscreens octyl methoxycinnamate and avobenzone. Similar results were obtained with uncoated microfine ZnO as well. These data show that, in finished formulation, these metal oxides not only caused no detectable break down of adjacent organic molecules but actually improved their survival.

In vitro cytotoxicity and photogenotoxicity studies. Studies have been conducted to determine the effects of TiO_2 on cell viability and other *in vitro* measures following irradiation. Interestingly, the potential therapeutic application of the photocatalytic potential of TiO_2 as an anticancer modality was the basis for some of these studies. Cai *et al.* (89) and Kubota *et al.* (90) found that TiO_2 particles exposed to UVR-killed tumor cells in culture or after transplantation to the backs of mice. The cytotoxic effects in either case were significantly reduced by free radical scavengers. The particles of TiO_2 were shown to be distributed intra- and extracellularly in these studies. Similar cytotoxic effects of irradiated TiO_2 was reported using human U937 monocytic leukemia cells by Huang *et al.* (91). Finally, in a study by Boehm *et al.* (92), it was found that irradiation of coated TiO_2 was less cytotoxic to human fibroblasts compared to uncoated TiO_2 .

Besides the lethal effects of irradiated TiO_2 on cultured cells, the consequence of this combination on genetic biomolecules has been investigated. In studies by Hidaka *et al.* (93), it was found that particles of TiO_2 irradiated with a mercury lamp could degrade solutions of naked DNA and RNA. Dunford *et al.* (94) reported that TiO_2 alone or in combination with ZnO oxidatively degraded phenol, a surrogate chemical, after irradiation. In this same study, it was found that both metal oxides produced DNA strand breaks, converting supercoiled plasmid DNA to a relaxed and ultimately linear form. Finally, these authors present semiquantitative results obtained in cultured human fibroblasts where TiO_2 produced DNA damage assessed using the comet assay. In all the experiments reported by Dunford *et al.* (94), it was found that the effects of irradiated TiO_2 could be reduced in the presence of free radical scavengers. In support of the studies by Dunford *et al.* (94) are the results of Nakagawa *et al.* (95) evaluating the photogenotoxicity of TiO_2 .

In single cell gel assays (*i.e.* comet assay) assessing DNA damage, the most pronounced effects were observed at cytotoxic doses of UVR + TiO₂. There was no effect of TiO₂ + UVR/visible light on microbial (*i.e.* photo Ames) or mammalian cell mutation assays. In these studies, there was an increase in chromosome aberrations occurring, again, at cytotoxic exposure of irradiated TiO₂. Collectively, these data are consistent with other *in vitro* studies demonstrating DNA damage at cytotoxic exposure to TiO₂ and UVR.

Acute in vivo studies. From the preceding discussion and as was the case with organic sunscreens, it logically follows that any putative cytotoxic/photomutagenic properties of TiO₂ would be expected to enhance UVR-induced skin damage *in vivo*. This hypothesis has been tested under acute and chronic conditions using hairless mice. In acute studies investigating UVR-induced DNA damage, both TiO₂ and ZnO applied to the skin of hairless mice prevented UVR-induced DNA damage (68,96). Thus, in contrast to the *in vitro* study results, TiO₂ and ZnO prevent the DNA damage produced by UVR in these *in vivo* studies.

Chronic in vivo studies. The hypothesis that TiO₂ may enhance UVR-induced damage has been investigated in chronic photocarcinogenicity studies in mice. In two separate studies, it was found that micronized TiO₂ substantially reduced UVR-induced tumor formation in mice (97,98). These data are consistent with the acute *in vivo* results and diametrically opposed to the seemingly logical extension of the *in vitro* studies. Simply stated, the *in vitro* studies do not predict chronic *in vivo* findings. Thus, considering the worst case using the most photocatalytically active metal oxide, TiO₂, there is no evidence that repeated application in the presence of UVR represents a potential human hazard under the conditions of these studies. To the contrary, *in vivo* experiments have shown the topical application of metal oxides as sunscreens to be beneficial.

Sunscreens studies in humans

Acute studies. The effect of sunscreens on the acute effects of UVR has been assessed in human skin. For example, Freeman *et al.* (99) found that a sunscreen containing OMC and benzophenone-3 protected human skin from UVR-induced DNA damage as evaluated by formation of pyrimidine dimers. The study by van Praag *et al.* (100) found a sunscreen containing the UVA filter, avobenzone, and the UVB filters, 3-(4'-methylbenzylidene)-camphor and 2-phenyl-benzimidazole-5-sulfonic acid, prevented UVB-induced cyclobutane dimer formation in human skin. Finally, PABA significantly reduced unscheduled DNA synthesis produced by high dose, 2 minimal erythema dose (MED), UVR exposure in human skin (101). Collectively, these data showing prevention by sunscreens of acute UVR-induced DNA damage *in vivo* support their protective benefit in humans. Moreover, despite the diverse methods and different endpoints, a singular favorable outcome was obtained.

The most recent human studies by Pontén *et al.* (102) and Kerkels *et al.* (103) have examined the effects of sunscreens on UVR-induced p53 expression taken from skin biopsies. Subjects exposed to UVR had an increase in p53 expression in the basal cell layer of unprotected skin. In both studies, application of a sunscreen significantly reduced p53-positive

cells. These authors conclude that p53 is a sensitive measure of UVR-induced DNA damage and that sunscreens protect against this effect.

Chronic studies. There is no direct evidence in humans that sunscreen use prevents nonmelanoma or melanoma skin cancers primarily due to the inability to conduct such a protracted study. However, in two prospective clinical studies it was found that repeated use of sunscreens suppresses the development of precancerous lesions (*i.e.* actinic or solar keratosis). Thompson *et al.* (104) found that regular use of a sunscreen containing OMC and avobenzone (tert-butylidibenzoylmethane) for 7 months prevented the development of solar keratoses in a dose-dependent manner. Because solar (actinic) keratoses are precursors of squamous cell carcinoma and a risk factor for basal cell carcinomas and melanoma (105), these data are suggestive that sunscreen use reduces the risk of skin cancers in the long term. Similarly, Naylor *et al.* (106) found that regular use of an SPF 29 sunscreen containing OMC, benzophenone-3 and octyl salicylate over 2 years significantly reduced cutaneous neoplasia, as indicated by its suppression of precancerous lesions. These data are the most direct evidence that use of sunscreen reduces the risk of NMSC in humans. Finally, the use of sunscreens has been reported to diminish some aspects of photoaging in humans (107). These data are supported by animal studies that have clearly established that sunscreens diminish photodamage (108–110). Thus, prospective clinical studies of sunscreen use by humans have found that regular, daily use reduces measures of chronic UVR-induced skin damage.

DISCUSSION

The most apparent acute benefit of currently available sunscreens is the prevention of sunburn from UVR exposure. This effect has been suggested to be both a benefit and a potential concern. The obvious benefit is the prevention of sunburn that may reduce the risk of nonmelanoma and perhaps melanoma skin cancers because severity and frequency of sunburns has been associated with NMSC formation (2,29,30). The concern has been inadequate protection of existing sunscreens and, more important, the potential for prolonged UVR exposure without acute signals (*i.e.* sunburn) ultimately leading to greater doses of UVA (111). Although the assumption that sunscreen use promotes or encourages prolonged sun exposure has not been substantiated with any data (112), it remains a popular view that is, in part, logical and appealing. Regardless, it should be noted that for a given acute UVR exposure, the skin damage produced in the absence of sunscreen photoprotection exceeds that obtained in their presence.

The human safety of current sunscreens

The most contentious views related to the safety of sunscreens have been built on *in vitro* findings using preparations of naked DNA or cultured cells. These studies have found that following irradiation, sunscreens may attack DNA either directly or indirectly *viz à viz* free radicals to produce damage in the form of adducts or cell death (56,58). From these results, it has been suggested that sunscreens may contribute to long-term skin damage. Specifically, it has been suggested that the DNA damage observed in these *in vitro*

studies may be carcinogenic and may result when sunscreens are used as directed. If the *in vitro* mechanisms have any basis for concern, then acute and, most important, chronic application should reflect these events and sunscreens should accelerate the appearance of UVR-induced DNA damage or tumor formation *in vivo*. As demonstrated, however, the *in vivo* results provide a singular answer that sunscreens protect against acute and chronic or delayed UVR-induced skin damage. For example, there was a trend toward delaying UV-induced tumor formation and decreasing the number of tumors per mouse in all photo-carcinogenicity studies conducted with sunscreens alone or in combination (Table 2). The singular outcome of these studies occurred despite methodological differences in all studies. The extent of protection by the sunscreens ranged from complete inhibition of UV-induced tumor formation to a delay in the appearance of tumors by 2–3 weeks. Thus, safety concerns based on current *in vitro* results with sunscreens have no bearing on the human use of sunscreens and may, in fact, be harmful to the extent that they discourage sunscreen use.

Why is there such a discrepancy between the *in vitro* and *in vivo* findings with sunscreens? Part of the answer, at least in the case of metal oxides, may be the proximity between sunscreen and cellular materials such as DNA *in vitro*. If the inorganic sunscreens are to participate in any of the reactions noted in the *in vitro* experiments, then the metal oxide particle itself must be present at the site of action. The metals, titanium or zinc, are not themselves photoactive. Most work studying metal oxide skin penetration has identified the metal, Ti or Zn, not the metal oxide, TiO_2 or ZnO . For instance, Ti has been shown in biopsies of clinical material analyzed by energy dispersive X-ray analysis or electron-probe microanalysis and from this, it has been inferred that TiO_2 can pass through skin (113–115). These findings include case studies and do not differentiate between TiO_2 and Ti and, as such, are far from conclusive. If TiO_2 was present, the possible route of entry is not at all clear and would warrant further study. Regardless, even if small amounts of TiO_2 do penetrate the skin, getting to a critical site of action, *i.e.* nucleus of basal cells in the skin, and receiving enough UVR, the likelihood of some biologically significant event seems unlikely.

As above, the penetration of Zn^{2+} has been studied and incorrectly interpreted as being indicative of ZnO penetration. A limited number of studies have found that Zn^{2+} from a ZnO -impregnated occlusive dressing penetrated wounded rodent skin (116–118) and human skin (118,119). Again, in these studies, Zn^{2+} not ZnO was analyzed. In the human studies, Zn^{2+} was measured from fluid of suction blisters, a procedure that compromises the barrier function of the skin. Other studies using more conventional approaches to assess human skin penetration have found no evidence of penetration of ZnO . Derry *et al.* (120) reported no significant percutaneous penetration of Zn^{2+} after topical application of 40% ZnO to humans. Dussert *et al.* (121) found no evidence of ZnO penetration as determined by TEM, a procedure that would have identified the actual presence of oxide particles. Finally, Vinson and Proch (122) found a negligible amount of Zn^{2+} , approximately 0.1% of the applied dose of ZnO , was absorbed after topical application under patch. In summary, the absorption of ZnO through intact human skin fol-

lowing topical application is nondetectable and that of Zn^{2+} is, at most, negligible. Under appropriate conditions, hydrolysis of ZnO likely accounts for any change in epidermal Zn^{2+} concentrations after topical administration. Importantly, Zn^{2+} has no redox potential under physiologic conditions, thus the relevance of its absorption is questionable, especially in light of the ubiquitous nature of Zn^{2+} in mammalian systems.

The question of permeability of human skin to inorganic sunscreens deserves a definitive study, using methods that are sensitive enough to detect very low levels of the metal oxides themselves that could be relevant to DNA damage. For the organic sunscreens, the penetration and metabolism of organic sunscreens requires additional studies. In addition, the photostability of the organic sunscreens is now becoming a concern although it appears to be most relevant to only one agent, avobenzone. Nonetheless, to date, the preclinical and clinical study results all support the human safety of the currently used organic and inorganic sunscreens.

Protected versus unprotected skin

When one applies a sunscreen, the attenuation spectrum of that sunscreen defines the spectrum of UVR to which underlying cells in the skin are subjected. In this way, sunscreens alter the light spectrum to which the skin is exposed. This sunscreen-protected spectrum (SPS) will depend on the kind of sunscreen used and, with the majority of sunscreen products currently available, it is certain that longer UVA wavelengths will comprise this SPS. It is for this reason that ideally we should know the complete action spectra, threshold and dose-response for any physiological, biological and molecular phenomena that occur in the skin. For example, the elucidation of skin immunology two decades ago led to a concern that even though sunscreens block the acute inflammation produced by UVR they might not prevent the immune-suppressive effects. Numerous studies have come down on different sides of this question (123,124). Different experimental conditions, including light sources and the lack of UVC filters, can account for many of the disagreements and the full story remains to be told because a complete action spectrum for immune suppression has not been described. Thus, it seems critical that UVR-mediated biological events be carefully characterized before the significance of UVR-sunscreen interactions can be fully understood.

Although sunscreens do not form an impervious barrier across the solar UVR spectrum, most currently marketed products absorb UVB very efficiently and hence prevent erythema very effectively as described by their SPF. Some sunscreens also contain UVA-absorbing chemicals. However, except for butylmethoxydibenzoylmethane (*i.e.* avobenzone) and the metal oxides of titanium and zinc, currently used sunscreens are not impervious to all UVA wavelengths. Some UVA filters absorb in the UVAIL region, ~320–360 nm (Table 3) but not in the long wavelengths of UVAIL. It is important to note that, as of this writing, the term broad spectrum can be used for sunscreen products in the United States containing UVAIL (320–340 nm) filters, even though, as previously noted, the majority of marketed sunscreen products do not contain UVAIL filters. Thus, cells in the skin, even if protected with a currently labeled broad-

Table 3. Attenuation spectra for commonly used UVR filters*

Ingredient	UVB	UVAII	UVAI
Octyl methoxycinnamate	+	—	—
Oxybenzone	+	—	—
Octyl salicylate	+	—	—
Octocrylene	+	+	—
2-Phenyl-benzimidazole-5-sulfonic acid	+	—	—
Menthyl anthranilate	—	+	—
Homosalate	+	—	—
Padimate O	+	—	—
Avobenzone	—	±	+
Microfine zinc oxide	+	+	+
Microfine titanium dioxide	+	—	±

* UVB: 290–320 nm; UVAII: 320–340 nm; UVAI: 340–400 nm.

spectrum sunscreen, can be exposed to biologically relevant doses of longer UVA wavelengths. Thus, we believe sunscreens need to be improved particularly in blocking longer UVA wavelengths. Nonetheless, given their broad benefits, we support the continued promotion of their recreational and daily use as part of a strategy to reduce UVR exposure with the desire of improving public health.

Sunscreen use and melanoma

It is well beyond the scope of this review to consider the role of sunscreen use and the prevention/causation of melanoma. However, it is necessary to mention considering the controversies surrounding this subject. In the most simple terms, if UVR exposure plays a role in the etiology of melanoma as suggested (2,33–35), then reducing sun exposure should diminish the risk of developing this skin cancer. Thus, sunscreens would by this definition be beneficial in reducing the risk of melanoma provided they are applied properly, on a regular basis and do not modify behavior leading to prolonged periods of sun exposure. Clearly, the lack of an animal model of melanoma has slowed our ability to understand the pathogenesis of this disease. There is an urgent need for more research in the causation of melanoma and prospective clinical studies of preventive approaches including the use of sunscreens.

The need for broad-spectrum UVB/UVA sunscreen products

There is growing evidence that although UVB is the most damaging component of sunlight, UVA is responsible for numerous morphological, molecular and biochemical events that may contribute to photodamage of skin (125–128). The effects of long-term UVA radiation have been reported to be different qualitatively and quantitatively from those of UVB (129–131). Finally, the mechanism(s)/chromophores by which these wavelengths affect biological processes are different. For example, UVB is believed to be absorbed primarily by DNA, RNA and proteins that may be the direct chromophores mediating the damaging effects of these wavelengths. In contrast, the effects of UVA are secondary to the formation of free radicals, and the chromophore(s) leading to the generation of these reactive oxygen species is unknown.

Emphasizing the need for broad-spectrum sunscreens, Diffey (132) calculated the UVA dose received with and without sunscreens. It was shown that 6 J/cm² of UVA would be absorbed by the skin (~20 min to receive 1 MED without a sunscreen). With an SPF-8 sunscreen containing a UVB absorber and a UVA absorber such as benzophenone, the time one could remain in the sun without developing erythema would be extended to 2.5–3 h. During this period, the skin would receive a total of 15 J/cm² of UVA. Studies have shown that repeated exposure to similar, suberythral doses of UVA produce skin damage (133). Thus, sunscreens should provide long wavelength, UVAI, photoprotection to reduce UVR-induced skin damage particularly if they have the potential to modify human behavior resulting in prolonged sun exposure.

UVA studies in humans. Chronic suberythral exposure to UVA appears to produce changes in human skin indicative of photoaging (133–135). Deleterious effects of suberythral doses of UVR have been reported previously in human studies by Kaidbey (136). After application of SPF-15 and -30 sunscreens, subjects were exposed to ~15 MED of SSR. Faint erythema developed in some of the SPF-15-protected sites but not in the SPF-30 sites. Although the greatest number of sun burn or apoptotic cells occurred with the former, they were induced in all subjects, even those protected with the SPF-30 sunscreen. The most noteworthy conclusion from these studies was that injury can also occur in human epidermal cells in the absence of erythema and with doses that are far below the SPF of the sunscreen. In another study, Pearse and Marks (137) applied an SPF-5 sunscreen to human skin and exposed sites to 2, 4 and 6 MED of UVB. Erythema was prevented in the 2 and 4 MED groups but skin thickening and epidermal enzyme activity were affected by the transmitted radiation (137). The latter observation emphasizes the need to understand the skin photobiology that results from the SPS.

Using a different approach, Lavker *et al.* (133) exposed human subjects, at different sites, to 0.5 MED of SSR (290–400 nm) and 0.5 MED of UVA (320–400 nm) (28 individual doses during a 5 week period). Compared to unirradiated skin, significant changes were observed including increased binding of lysozyme to elastic fibers, suggesting some change in the fibers and increased inflammation as determined by leukocyte common antigen deposition. Similar changes were produced by both spectra with the greatest effect seen with UVA. Lavker *et al.* (134) extended these findings showing that the dose-dependent changes in lysozyme deposition, inflammation and hyperplasia produced by broadband UVA were produced equally by UVAI, suggesting that these longer UVA wavelengths play a significant role in UVR-induced skin damage.

Chronic UVA studies in rodents. In a recent study conducted in hairless mice, Kligman *et al.* (83) showed that with respect to the deleterious effects of chronic exposure to SSR, it is not sufficient merely to prevent acute UVB-mediated skin responses but that full-spectrum protection is essential. These studies were performed assuming that use of high SPF products will modify human behavior, resulting in prolonged solar UVR exposure because erythema was prevented. Thus, the SPF of the sunscreen was used to determine the UV dose. It was shown that a UVB-absorbing sunscreen (SPF-

7) allowed the greatest damage to the epidermis and connective tissue matrix even though none of the animals developed an acute skin response. The authors reported that dermal connective tissue was especially vulnerable to the small amounts of transmitted radiation in these studies. It was shown that protection was significantly increased with an SPF-16 sunscreen that contained, in addition to the UVB absorber, a UVAII absorber and an erythema protection factor more than twice that of the UV dose delivered. An SPF-18 sunscreen, with the addition of the UVAI absorber (340–400 nm; peak absorption 355 nm) provided the most effective protection.

Photocarcinogenesis has been reported following repeated exposure to UVA in rodents (138,139). In addition, Setlow *et al.* (140) has determined the action spectra for melanoma in fish and shown that wavelengths of light as long as 450 nm, with a peak at 365 nm, can induce tumor formation. Setlow *et al.* have suggested that the contribution of large amounts of longer wavelength UVA and even visible photons could contribute to melanoma even in sunscreen-protected skin. While some critics have questioned the relevance of applying animal studies to human photobiology, these data are suggestive that UVA is biologically important.

Collectively, these studies point to the need for UVA photoprotection. These data raise the question of identifying chromophores for longer UVA wavelengths and possibly shorter visible light wavelengths. While this is an often touted feature of action spectra determinations, it is rare to be able to specify an actual chromophore; however, such studies do indicate which wavelengths have potentiating effects.

CONCLUSIONS

UVR exposure is causally linked to NMSC and may play a role in melanoma. Sunscreens unequivocally and reliably decrease the amount of UVR to which the skin is exposed. Past and most current sunscreens provide excellent UVB protection but lack UVA, especially UVAI, attenuating ingredients. Newer sunscreens are being formulated to cover virtually the entire UV spectrum by incorporating recently available long UVA blocking ingredients.

Although continued investigations will certainly be fruitful, existing *in vivo* animal and human studies are remarkably consistent in their conclusion that sunscreens are both safe and effective. Again, one criticism has been that sunscreens block only a portion of the UVR spectrum. Now that true broad-spectrum protection is possible, this should no longer be an issue.

Where sunscreens may pose a danger, however, is in their ability to change behavior and turn us into "mad dogs and Englishmen" that go out into the noonday sun. As such, sunscreens are only part of a sensible sun protection strategy that must include proper clothing, hats, sunglasses, sun avoidance during peak hours and, most importantly, education. Until the notion of a healthy tan is eliminated from the western psyche, we believe the current skin cancer epidemic will continue.

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