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A Research on Sunscreen Safety and Efficacy

Madake Dhiraj Uddhav[1*] and Swagati Moon R[2]

Department of Chemistry, Pratibhatai Pawar College of Pharmacy, Shrirampur, India

[*]***Corresponding author:*** *Madake Dhiraj Uddhav, Department of Chemistry, Pratibhatai Pawar College of Pharmacy, Shrirampur, India, E-mail: dhirajmadake1001@gmail.com*

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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 nm-320 nm) filters. The SPF test, however, does not adequately assess the complete photo protective profile of sunscreens specifically against long wavelength UVAI (340 nm-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 photo protection.

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, sub chronic 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.

Keywords: Photo protection; UVA efficacy; Wavelength; Ultraviolet radiation

INTRODUCTION

The incidence of nonmelanoma and melanoma skin cancers has been increasing in most parts of the world for several decades. Exposure to UV radiation (UVR)? from the sun plays a causal role in acute and chronic skin damage including skin cancers. 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 nm-320 nm) and in some cases, short wavelength UVAII (320 nm-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 [1].

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 [2].

LITERATURE REVIEW

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, pigmentation (hyperplasia, immunosuppression and vitamin D synthesis) and chronic effects, primarily photo carcinogenesis and photo aging. 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 and in the most empirical terms sunscreens reduce the dose of UVR (Figure 1) [3].

Figure 1: 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.
- The incidence of NMSC is inversely related to latitude in populations of mainly European origin and is greater in outdoor compared to indoor workers.
- The NMSC is most common on the head, neck, arms and hands, areas of the body that receive the largest dose of UVR.
- Persons that easily sunburn, *i.e.*, fitzpatrick skin types I and 11, are more susceptible to the development of NMSC 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.

Evidence for a role of UVR in photo aging

Like skin cancer, chronic exposure to solar UVR is thought to accelerate aging of human skin. This skin photo aging is characterized by dryness, roughness, irregular pigmentation such as freckling/lentigenes, actinic keratoses, wrinkling, elastosis, inelasticity and sebaceous hyperplasia. The incidence and severity of skin photo aging 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 photo aging than women with a low UVR exposure history. 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. 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 [4].

Sunscreens as part of a photo protection strategy

Sunscreen mediated photo protection 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.

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:

- Anthranilates
- Benzophenones
- Camphors
- Cinnamates
- Dibenzoylmethanes
- p-aminobenzoates
- Salicylates

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.

Inorganic sunscreens

During this decade, the inorganic sunscreens have been used with increasing frequency in beach and daily use photo protection 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 (TiO_2) and Zinc Oxide (ZnO). Although these two metal oxides differ substantially in their appearance and attenuation spectra, they share some general properties that are discussed briefly. Zinc oxide and TiO, exist as odorless white powders comprised of a Gausian or normal distribution of particle sizes. Micro fine powders, used in sunscreen products, have an average particle size of approximately 0.20 pm (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, micro fine 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, micro fine powders have always been present in ZnO or TiO, containing products but were optically overwhelmed by the larger particles. Thus, micro fine particles do not represent an entirely new particle size, just a refinement of the existing particle size distribution. Each particulate has a size at which it maximally scatters visible light. 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 micro fine grades of metal oxides that are now being widely used in sunscreen and daily skin care formulations [5].

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 photo protection 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 [6].

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 (Figure 2).

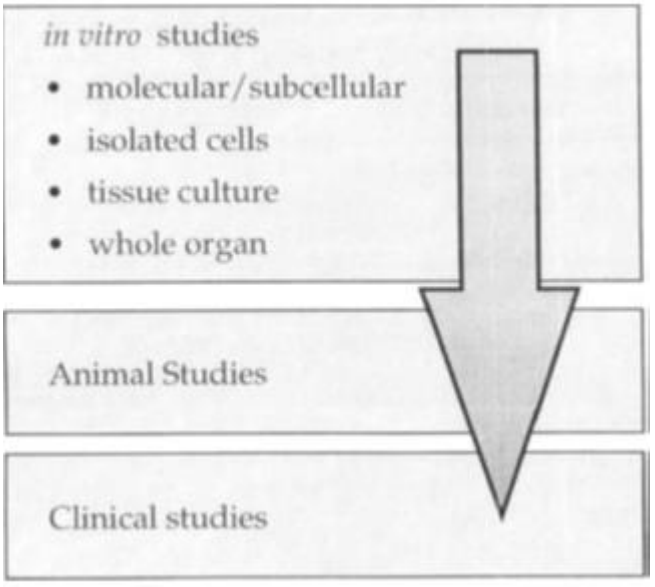

Figure 2: Toxicological hierarchy in assessment of human risk. This cartoon represents different levels of human relevance from a toxicological view point. Results from *in vitro* studies need to be balanced against animal and clinical studies when considering risk to human health.

Studies with organic sun screens

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 0) and amyl p-dimethylaminobenzoate (Padimate A) were developed and utilized during the 1960's and 1970's. 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 Acute *in vivo* studies. From the *in vitro* study result 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 and Walter and DeQuoy 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 reported that Octyl Methoxycinnamate (OMC), the most common UVB sunscreen used in the world and terephthalylidene dicamphor sulfonic acid, a UVBAJVA 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. Ananthaswamy, et al., 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.

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. They conducted a series of experiments with mice to determine the effect of a benzophenone derivative, 3-benzoyl-4-hydroxy-6-methoxybenzenesulfonic acid 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 and Flindt-Hansen et al., that found topical treatment with PABA significantly reduced the tumorigenic effects of UVR in mice. Furthermore, Flindt-Hansen et al., 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 photo mutations 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 [7].

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. The concern has been inadequate protection of existing sunscreens and more important, the potential for prolonged UVR exposure without acute signals (*i.e.*, sunbum) ultimately leading to greater doses of UVA. Although the assumption that sunscreen use promotes or encourages prolonged sun exposure has not been substantiated with any data, 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 photo protection exceeds that obtained in their presence [8].

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 an indirectly viz u viz free radical to produce damage in the form of adducts or cell death. 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-cocarcinogenicity studies conducted with sunscreens alone or in combination. 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. 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. 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 [9].

Sunscreen use and melanoma

It is well beyond the scope of this review to consider the role of sunscreen use and the preventiodcausation of melanoma. However, it is necessary to mention considering the controversies surrounding this subject. In the simplest terms, if UVR exposure plays a role in the etiology of melanoma as suggested, 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 [10].

CONCLUSION

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 photo damage of skin. The effects of long-term UVA radiation have been reported to be different qualitatively and quantitatively from those of UVB. 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.

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