











POSITION STATEMENT

Photoprotection of the future: challenges and opportunities

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Abstract

The use of sunscreens is an important and essential component of photoprotection. Since their introduction during the first half of the last century, sunscreens have benefited enormously from major technological advances such as the development of novel UV filters; as a result, their efficacy in preventing UV-induced erythema is unequivocal. More recently, however, new challenges have appeared, which have prompted a robust discussion about the safety of sunscreens. These include topics directly related to photoprotection of human skin such as improved/alternative methods for standardization of assessment of the efficacy of sunscreens, but also many others such as photoprotection beyond UV, concerns about human toxicity and ecological safety, the potential of oral photoprotective measures, consequences of innovative galenic formulations. On a first glance, some of these might raise questions and doubts among dermatologists, physicians and the general public about the use sunscreens as a means of photoprotection. This situation has prompted us to critically review such challenges, but also opportunities, based on existing scientific evidence. We conclude by providing our vision about how such challenges can be met best in the future in an attempt to create the ideal sunscreen, which should provide adequate and balanced protection and be easy and safe to use.

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Conflicts of interest

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Introduction

Mankind has been protecting itself from the sun and its effects for centuries, but it was not before the middle of the last century that the Austrian Franz Greiter, the American Benjamin Green and the French Eugène Schueller developed the modern sunscreen. Whereas Schueller launched 'Ambre Solaire' in 1936, Greiter's and Green's products became commercially available in 1946 and 1956, respectively.¹ Over the following decades, remarkable advances in skin biology, photobiology and epidemiology of skin cancers have led to a greater understanding of the role of different wavelengths in photocarcinogenesis, photoaging and photodermatoses. One important discovery was that both UVB and UVA rays can damage human skin and as a consequence industry developed broad-spectrum sunscreens, which provide protection against UVB and UVA radiation.

Sunscreens were initially developed to protect from sunburn, that is, acute damage resulting from exposure to sunlight. As the relation between solar exposure and skin cancers became understood, sunscreen use also became an important part of the general strategy for the prevention of skin cancer, which also includes seeking shade, wearing photoprotective clothing, wide-brimmed hat and sunglasses. The importance of sunscreen use in prevention of skin cancers, especially squamous cell carcinoma, is unequivocal as evidenced through several studies.^{2–6} Similarly, sunscreens are also effective contributors in providing protection against UV-induced dyspigmentation, photoaging and photodermatoses.^{7,8} Photoprotection and the use of sunscreens have therefore been promoted in public health campaigning as part of healthy sun-related behaviours and, in fact, is constantly increasing. With the onset of global warming and the resulting increase in the number of very sunny, long-lasting weather periods all over the world, this development is likely to continue, making photoprotection and regular sunscreen use even more important.

However, recent years have also witnessed rise of controversies regarding the safety and efficacy of sunscreens. In many cases, these controversies lack a scientific basis. In particular with the onset of the age of the Internet and social media, consumers are regularly bombarded with information that is not always scientifically sound. This poses the risk that a part of the population might put in doubt the real 'need' for sunscreens and question their safety. In the absence of a clear message from their healthcare provider, consumers may decide to discontinue sunscreen use leading to increasing number of persons that are not

adequately protected against solar exposure. In this regard, healthcare providers are in a pivotal position to resolve doubts and provide evidence-based answers to these questions related to sunscreens and advocate the appropriate photoprotection measures. Research shows indeed that their counselling can have a positive impact on the protection habits.⁹ In other cases, however, such controversies might point to weaknesses and limitations of currently used sunscreens, which do have a scientific basis and which therefore should be addressed. Also, modern sunscreens are subject to technological progress which is no longer limited to the development of novel UV filters, and this also greatly impacts their efficacy and safety. Thus, it is time to revisit the established precepts regarding sunscreens in order to improve on the existing concepts and develop a vision of what should be the ideal future sunscreen.

In this context, six leading dermatologists from Europe, United States and South America, together with experts in toxicology, regulatory aspects and SPF testing methodology of sunscreens, came together to review the current challenges and opportunities in photoprotection. The essentials of this discussion are summarized in this viewpoint paper that concludes with concrete recommendations on what would constitute an ideal future sunscreen.

SPF Testing to determine protection against erythema

Sunscreens are most commonly characterized by their sun protection factor (SPF) value which is an easily recognizable indication of level of protection provided by the product. The standardized SPF testing methods (FDA 2011, ISO 24444:2010) measure the minimal UV doses inducing erythema (MED) with a xenon arc solar simulator with defined spectral distribution and total irradiance. These testing methods are different from sunscreen use in real life conditions with varying conditions of climate and geography where the exposure to radiation varies.

It should be noted that current SPF testing methods, though greatly harmonized, are still beset with endpoint and method-driven variability in results, and hence, SPF values obtained.¹⁰ The establishment of erythema is the primary endpoint for SPF determination by current methodology. However, what constitutes erythema can be interpreted differently as per the internal criteria of the different testing laboratories. Standardization of erythema scoring by using defined colour-based scale could add objectivity to these measurements. This criterion indirectly impacts the irradiation doses employed to generate erythema as

a more intense erythema may require a higher radiation dose in a relatively short time. Irradiation doses used for testing are indeed important because testing of certain sunscreens following the ISO methodology using higher irradiation dose regimens was found to greatly underestimate the real use protection against erythema.¹¹ Added to that are the inherent differences in MED for volunteers depending on gender, age, phototype, ethnicity, etc. SPF testing is usually conducted with volunteers with Fitzpatrick skin types I-III because they have shorter irradiation times and MED determination is easier. However, a predilection for choosing these volunteers may be leading to overestimation of SPF values for products. Damian *et al.*¹² reported that MED correlated negatively with SPF; volunteers with lower MEDs produced higher SPFs. Differences between radiation sources and non-homogenous application of product may also increase inter-laboratory variability.¹³ In this scenario, the real life protection provided by the product may be under or overestimated due to the particularities of the testing site.

It would therefore be important to introduce improvements on the existing method to limit the sources of variability, for example the use of chromametry to determine the individual typology angle (ITA) to classify skin phototypes in a more objective manner than the current Fitzpatrick based classification. The ongoing revision of the ISO 2444:2010 is already incorporating this new system.

Several alternative endpoints, other than erythema, reflecting both acute and chronic effects have been proposed in the literature. These 'other protection factors' such as immune protection factor, integral sun protection factor, free radical skin protection factor and p53-related cancer protection factor were recently reviewed by Osterwalder and Herzog.¹⁰ Hybrid diffusion reflectance spectroscopy¹⁴ and *in vitro* SPF methods are other non-erythema options for studying sunscreen efficacy, which are currently under evaluation by ISO Sun Protection Test Methods.

In spite of these limitations, SPF testing method is still the only method available to test and communicate the level of protection against erythema offered by sunscreens. Current FDA and EC recommendations limit the labelled SPF factor to 50+. The rationale behind this rule is the limited benefit provided by SPF 100 over SPF 50 sunscreen, the high variability in SPF determination for products with higher SPF, and the potential for misleading consumer interpretation of SPF 100 as 100% protection. However, several recent studies report benefits of SPF 100 sunscreens compared against SPF 50+ sunscreens in real life conditions. These differences are most likely due to under-application of sunscreen products by the study subjects, who applied 0.5–0.8 mg rather than 2 mg/cm², which is the amount used in SPF testing.^{15,16} Under these conditions, SPF 100 sunscreens provide a real use SPF of approx. 25 and thus offer higher protection recommended for reducing skin cancer as defined by FDA, that is an SPF of 15. In contrast, SPF 50 products provide a real protection of only 12.5, which is below the FDA threshold

for skin cancer prevention. As a consequence, FDA, in the latest proposal in February 2019, has now proposed to cap the SPF at 60+ (pending final ruling in Nov. 2019). In Mercosur, sunscreens may be labelled with SPF from 6 to 99.¹⁷

UVA protection

The consumer perception of SPF factor as the single most important reference defining sunscreen protection is probably responsible for the protection in non-UVB part of the spectrum lagging behind. UVA radiation is implicated in photoaging,⁷ pigmentary disorders,⁸ melanoma and many photodermatoses¹⁸ and as such adequate protection against it is essential. This is especially relevant for individuals with skin of colour as they are more susceptible to pigmentary changes.¹⁹ Although most broad-spectrum sunscreens provide UVA protection, providing protection against long wavelength UVA continues to be a significant issue and this needs to be addressed. In the United States, another problem is that there are fewer FDA approved filters to work with compared to other parts of the world. Another challenge for UVA protection is the communication of the level of protection provided by sunscreens on the label and harmonization of the same on a global level. Currently, a numerical indication of UVA protection is not provided on the label. The closest approximation to a numerical indication is perhaps the European and South American label where the term UVA within a circle indicates that the protection level against UVA is at least one-third of the protection level against UVB. In light of growing knowledge about harmful effects of UVA and the susceptibility of certain subsets of populations to UVA, this situation is far from optimal and needs to be improved and worldwide harmonization in testing methods used and numeric communication on the label needs to be implemented.

Protection against wavelengths beyond UV

In the past, the non-UV spectrum of solar radiation was considered to have no relevant adverse biological effects on skin. Today, we know that this assumption was incorrect because such wavelengths clearly impact skin and modern sunscreens should therefore offer protection against longwave UVA (UVA1, 340–400 nm) and non-UV radiation such as visible light (VL) and near infrared (IR). VL has been shown to result in long-lasting skin pigmentation in individuals with skin of colour but not in fair-skinned subjects.²⁰ Furthermore, this effect is significantly potentiated by even a small percentage (0.44%) of UVA 1 covering 340–400 nm.²¹ Subsequent studies showed that the action spectra is in the blue and violet wavelength range²² and that opsin3 receptor-mediated increase in melanogenesis and increased activity and/or stability of multimeric TYR/P protein complexes are responsible for the long-lasting skin hyperpigmentation seen in skin types III-VI.²³ VL might also contribute to the pathogenesis of melasma²⁴ and postinflammatory hyperpigmentation.²⁵ Studies suggest that incorporation of physical

shields such as iron oxides in sunscreens will protect skin from solar radiation-induced hyperpigmentation.^{26–28} Such products, however, are tinted, that is visible to the consumer, and thus are not optimal from a compliance point of view. Of note, topical antioxidants do not provide protection against VL-induced skin pigmentation and related product claims have the potential to mislead consumers.²³

In case of IRA, the biological effects on skin are mediated by oxidative stress and/or heat accompanied by upregulation of matrix metalloproteinase-1 (MMP-1) expression in the dermis, which effectively degrades collagen and promotes wrinkle formation.²⁹ Increased wrinkle formation was clearly shown in IRA-exposed hairless mice, and the concomitant increase in MMP-1 expression following IRA exposure and its prevention by sunscreens containing antioxidants was also demonstrated in randomized, vehicle-controlled human studies.³⁰

Balance of wavelength-specific protection

Unbalanced protection against UVA vs. UVB is a limitation of many of the currently available sunscreens today. A consequence of high SPF and low UVA protection sunscreen products, in addition to choosing erythema as the main endpoint pose an inherent danger that people tend to stay in the sun longer, thus increasing their exposure to UVA and other wavelengths of the solar spectrum. Diffey has indicated that a modern sunscreen should provide a balanced spectral absorption in line with protection provided by shade and many types of clothing fabric.³¹

Additionally, if and to what extent a sunscreen should protect against a certain part of the spectrum needs to be discussed by taking into account the respective health effects. Whereas for UVA, there are clear health effects and adequate protection should be provided, for VL, the health effects seem to be limited to pigmentation and attributable mainly to high-energy blue-violet light (HEVL).²² Protection against VL is most relevant for individuals with skin of colour who are more prone to develop with pigmented disorders such as melasma and post inflammatory hyperpigmentation (PIH).³² These health effects are seen at high dose and irradiance, which are typically found in natural sunlight. They are not present in VL emitted from screens.³³ For IRA radiation, published data indicate a relationship between IRA and photoaging, in particular wrinkle formation. According to the best of our knowledge, neither VL nor IRA seems to be directly associated with skin cancer. In the opinion of this group, for effective photo-protection it is important to consider the solar spectrum as a whole. We here would like to emphasize that there is a lack of knowledge regarding the relevance of the interaction between radiations of different wavelengths constituting the solar spectrum. Indeed, very preliminary studies indicate that such interactions might occur, for example between UVB and UVA rays when applied simultaneously at ratios which are relevant for natural sunlight, and that the resulting biological response is different from the one induced by UVB or UVA individually.³⁴

Outdoor testing, where subjects are exposed to solar light in its entirety with full spectrum under controlled conditions, is a good opportunity to learn about the real performance of sunscreens and sunscreen-related behaviours. However, factors such as exposure, UV index, latitude and weather all play a role in interpretation of endpoints and the logistics of conducting such a study can be very complex. Some conditions, however, such as those used in the glacier study³⁵ need special consideration as the effects of reflected radiation cannot be recreated in the lab, indicating that in some aspects, outdoor studies are clearly superior to indoor testing. Accordingly, when comparing two products with similar SPF value on the label, factors such as heat and photostability of the product can create differences between the two products, which may be highlighted under real life conditions, yet not be apparent in indoor studies.³⁶ Clearly, outdoor testing, even when standardized, would not be viable for routine testing of sunscreens, but we believe that it represents a valuable strategy to further address and possibly resolve controversies concerning sunscreen efficacy and safety which cannot be clarified by indoor testing.

Safety – myths and reality

Although sunscreens have been in use since the 70s there have been no reports of negative systemic effects of organic filters in humans. Though we are fully aware of the issues regarding the endocrine disruption potential of certain organic filters in animal models, it has to be noted that standardized tests to evaluate truly the potential of a UV filter as an endocrine disruptor are not available. Some of the published data on the endocrine disrupting potential of commercially used UV filters was obtained from *in vitro* and animal studies that are not easily extrapolated to humans. Of note, a recently published study has reported the penetration of topically applied organic filters into the blood circulation of human subjects. Specifically, after 75% body surface application at maximal usage conditions, organic filters were absorbed and had detectable plasma levels.³⁷ However, the clinical relevance of these findings is completely unknown. Further studies are needed to understand the impact of this information on the safety of organic filters. Inorganic filters generally enjoy a more positive safety profile but the possible dermal penetration of nanoscale inorganic filters through intact or sunburned skin is controversial. Today, some evidence suggests that this may be unlikely^{38–40}; however, further research may help provide more clarity.

Another safety concern that has introduced a doubt in the consumers mind regarding sunscreens is the decline in levels of vitamin D in plasma, which can occur as a result from reduced exposure of sunscreen protected skin to UVB. Two recently published articles reviewed the evidence on the impact of sunscreen use and vitamin D status and concluded that sensible use of daily broad-spectrum sunscreens with high UVA protection will not compromise vitamin D status in healthy people.^{41,42} However,

in some persons, rigorous photoprotection behaviour including use of high SPF sunscreens with high UVA protection along with protective clothing and shade seeking are likely associated with compromised vitamin D status. Such a vitamin D deficiency can easily be overcome, however, by oral vitamin D supplementation. In aggregate, UV radiation is a complete carcinogen, and this clearly outweighs any concerns regarding a potential decrease in vitamin D levels.

Long-time use of facial sunscreen has lately been linked to frontal fibrosing alopecia (FFA), reported mainly in women with long history of sunscreen use on the face, close to the hairline. Though first reported in 1994, recent years have seen an increase in the number of cases that are reported. At the writing of this manuscript, data are not conclusive.^{43,44} Patients using facial sunscreen year-around daily should be advised to apply generously but to avoid the areas with hair such as eyebrows and the hairline.

Cosmetic properties of sunscreens

One important challenge for sunscreens of the future is to ensure compliance and a general good adherence to photoprotection.⁴⁵ Factors like easy-to-use formats including ultra-light textures, convenient sprays and non-greasy formulations are key to encourage the regular use of sunscreens.⁴⁶ Good ocular safety for a facial sunscreen is important as stinging eyes is one of the main cited reasons for not using sunscreens while engaging in outdoor activities.⁴⁷ For darker skin tones, transparency in a sunscreen is important as white residues after application are not desirable. For those using make-up, it is important to have sunscreen options compatible with the application of colour cosmetics. Compact cream sunscreens can be a good option for persons wearing makeup to reapply sunscreen over the make-up throughout the day if needed. We also believe that sunscreens should have secondary cosmetic benefits which extend beyond their role in providing photoprotection, since this would also greatly stimulate their regular use.

Sunscreens and the environment

Public concern on the effects of sunscreens on the marine environment has garnered much attention in recent years, specifically the effects on coral reefs. Although scientifically sound information regarding the effects of UV filters on the environment is still scarce, the public consciousness regarding this is on the increase. A prominent example is the recent bans in Hawaii and Palau of sunscreens with certain organic UV filters in an effort to protect coral populations. Marine coral populations are highly labile to several environmental stressors such as increasing water temperatures of the oceans, detergent residues and other contaminants. Further research is needed to understand the toxicity of UV filters on corals.^{48,49} It might thus be that the changes required to slow global warming may seem too daunting to the average person compared with giving up the use of certain

sunscreens. In addition to coral reefs, environmental concerns of sunscreens include bioaccumulation and bio-persistence of certain poorly biodegradable UV filters, which can be found in fish and hence potentially enter the food chain. The downside of these measures and the resulting propaganda, however, is that they threaten the painstaking work done by public health campaigns advising adequate solar protection over the last several decades. In other words, public concerns about environmental safety of sunscreens, whether scientifically justified or not, need to be addressed in order to avoid a reduction in sunscreen use by the consumer.

At the same time, environmental safety must be considered when formulating sunscreens. This should be done by favoring, when possible, UV filters with more eco-friendly profiles and – in particular – by reducing the quantities of these used. Research efforts in identifying new UV filter molecules with low environmental impact as well as innovative ingredients which can be used together with and/or alternatively to UV filters to provide photoprotection should be combined with industry initiatives and regulatory support which would be essential in these new molecules getting regulatory approvals globally.

Potential for oral and systemic photoprotection

Nutritional supplements may contain one or more actives that promote skin photoprotection through different mechanisms and could thereby complement topical sunscreens. As an example, oral intake of nicotinamide prevents photo-immunosuppression and development of actinic keratoses and keratinocyte cancers in humans,^{50,51} and oral intake of carotenoids, or *Polydodium leucocotmos* can reduce UVB-induced erythema.^{52,53} We believe that the photoprotective potential of oral photoprotection has not yet been fully realized and should be further investigated. For regulatory reasons, in the past the emphasis has been on the prevention of UVB-induced erythema, similar to sunscreens. More recent studies indicate, however, that nutritional supplements which have a relatively limited efficacy to protect against UVB-induced erythema might perform much better if tested for their capacity to protect against UVA-induced skin damage.⁵⁴ This might, at least partially, be explained by the fact that nutritional supplements such as carotenoids can act as antioxidants. Accordingly, UVB-induced erythema mainly results from the direct generation of DNA damage, that is cyclobutane pyrimidine dimers (CPDs), by UVB, whereas UVA effects are mediated to a large extent by oxidative stress.^{19,55}

Systemic photoprotection can also be achieved by drugs. Afamelanotide (Scenesse®) is a first-in-class synthetic analog of α -melanocyte stimulating hormone, indicated for persons with inherited cutaneous porphyrias such as erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLPP) characterized by acute photosensitivity, resulting in reduced quality of life. Afamelanotide mimics the naturally occurring hormone to increase skin pigmentation by increasing melanin production in

melanocytes, resulting in increased sunlight tolerance in patients with EPP.⁵⁶

Targeted/personalized sunscreens

We clearly see a need for making photoprotection more targeted with the overall goal to provide better protection to susceptible groups within the general population. Differences determining susceptibility towards solar radiation are, for example confined by interindividual differences in solar radiation-induced generation of CPDs and/or the capacity to repair such DNA damage. As an example, recent publications suggest that UVA exposure can lead to the formation of 'dark' CPDs. The CPDs are DNA photoproducts that if not repaired can lead to mutations and ultimately to skin cancer. For the generation of dark CPDs, studies in mouse model showed that pheomelanin rather than eumelanin may be the more relevant form of melanin in this process,⁵⁷ suggesting that individuals with more pheomelanin (e.g. fair, red-haired individuals) might be more prone to develop this type of DNA lesions. Also, repair of CPDs is linked to individual MEDs and thus Fitzpatrick skin type. In darker-skinned people (Fitzpatrick skin types V-VI), DNA repair is more efficient than in fairer skinned people.⁵⁸ On the other hand, these skin types are more susceptible to VL-induced hyperpigmentation.^{20,22} We believe that future sunscreens ought to mold more closely to the individual needs of the consumers depending on their age, skin type, physiology, sun exposure behaviour and disease risks. Personalized photoprotection based on genetic profiling and identification of particular susceptibility factors of consumers is an exciting new area of research, which is likely to strongly influence the development of novel sunscreens in the near future.

The sunscreen of the future – our recommendations

It is clear that as our knowledge regarding the effects of solar radiation on the human organism is better delineated, the characteristics and role of sunscreens will have to constantly evolve in parallel.

Based on the previously discussed issues, concerns, developments and opportunities, we ask that an ideal sunscreen would provide protection against all wavelengths of natural sunlight with no safety concerns and minimum environmental impact with properties to ensure highest possible compliance. This might be achieved through the following steps:

- 1 SPF determination methodologies should evolve to predict sunscreen efficacy in real life conditions in a more reliable manner.
- 2 For SPF determination, alternative endpoints, other than erythema, reflecting both acute and chronic damage should be considered.
- 3 Photoprotection needs to include protection against wavelengths beyond UV.

- 4 Photoprotection should be balanced and should take into account interactions between different wavelengths in natural sunlight.
- 5 Efforts should be made to develop targeted/customized sunscreens for different population subgroups with different protection needs.
- 6 Continuous efforts need to be taken to improve compliance of regular sunscreen use by improving the textures, feel and delivery systems.
- 7 From a safety perspective, the concentration of UV filters should be as low as possible, and sunscreens should be formulated to have minimum environmental impact.
- 8 This can partially be accomplished by innovative ingredients to complement the protection provided by UV filters.
- 9 Sunscreen products with additional skincare benefits, such as hydration and rejuvenating or anti-aging properties, are needed to further encourage regular use by simplification of skincare routine.

The sunscreen of the future that encompasses the above characteristics will be a complex and a sophisticated product supported by robust scientific evidence gathered from controlled clinical trials and validated in *in vitro/ex vivo* tests. Such a sunscreen would have to be accompanied by continuous consumer education regarding risks and benefits. Sunscreen labels should communicate the essential information to the consumers in an easy-to-understand manner to enable the consumers to make an educated decision when choosing a sunscreen. The consumer should also be reminded that sunscreens are only a part, albeit an important part, of the overall strategy to reduce sun exposure. Photoprotection with topical sunscreens should be supplemented with seeking shade when outdoor, and the use of protective clothing, including hats and sunglasses. As data evolve, oral photoprotection could also be an addition of the overall photoprotection strategy.

For an ageing global population, the increasing incidence of skin cancer is a serious public health concern. In addition, the lay consumer is also increasingly concerned about photoaging and its effect on quality of life/healthy skin aging. In view of a general proclivity for outdoor activities, the need and role for topical photoprotection are well established. In view of these challenges, the sunscreen of the future should provide complete, but balanced protection, and it should be safe and easy to use.

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