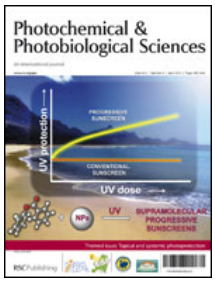


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## Topical and systemic photoprotection

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### Behaviour and measurement



### Topical photoprotection



### Systemic photoprotection

# The long way towards the ideal sunscreen—where we stand and what still needs to be done

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The magnitude and quality of UV protection provided by topical sun products have improved considerably over the past three decades. As our knowledge and understanding of sun protection requirements increases, product and testing technologies advance and new sunscreen molecules and technologies become available. The biannual London Sun Protection Conference has monitored this development over the last two decades. The 2009 edition of the conference (June 3 and 4) was entitled "Perfection of Protection". This paper, based on our talk given at the conference, tries to answer the question about the "ideal sunscreen" and explores four key requirements of good UV protection regarding where we stand on a ranking scale between poor and perfect, and what still needs to be done. Technology is leading with a rating of 80%, Assessment/measurement follows at 70%, Norms/standards around 50% and Compliance ranks only around 30% between poor and perfect. UV filters are the heart of the product technology. Besides UVB-filters, plenty of UV filters for UVA II and UVA I protection are now available in most parts of the world, except the USA. Although the Sun Protection Factor is well established and various methods have been developed for assessment of UVA protection, the performance measurement of sunscreens is still far from perfect. On the other hand, the high bar for achieving the highest UVA protection in the various classification systems released recently in Europe (2006) and the USA (2007) already helped to increase the protection considerably. The greatest problem however, remains poor compliance. Providing cosmetically pleasing formulations that people like to wear and communicating what sunscreens are and how they work are key elements in improving UV protection.

## Introduction

The level and quality of UV protection provided by topical sun products have improved considerably over the past three decades. In parallel to the increase of our knowledge and understanding of protection requirements, product and testing technologies advanced and new sunscreen molecules and technologies became available. The biannual London Sun Protection Conference has monitored this development over the last two decades. The 2009 edition of the conference (June 3 and 4) was entitled "Perfection of Protection". This paper is based on our talk given at the conference, entitled "The Long Way Towards the Ideal Sunscreen—Where We Stand and What Still Needs to Be Done".[1] We asked the question what is the "ideal sunscreen" and what are the requirements for good UV protection. The ideal sunscreen protects against sunburn, skin photo-aging and skin cancer during lifetime sun exposure. The question is which grade of optical density and which spectral protection profile are necessary to achieve this goal. We identified four key requirements for good UV protection:

– Technology
– Assessment/measurement methods
– Norms and standards
– Compliance

These key requirements are all related to each other and influenced by many stakeholders (Fig. 1). Technology alone cannot guarantee good UV protection. The performance of a sunscreen has to be measured and benchmarks have to be set in the form of norms or standards by authorities or the industry itself. All this is still not sufficient if the user of the product does not apply it properly or at all. The compliance of the consumer or patient that wants to protect him- or herself does

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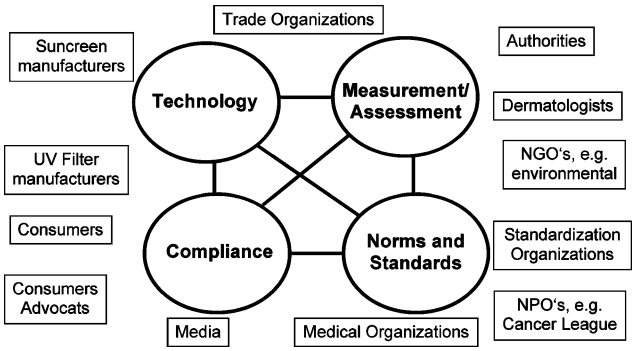



**Fig. 1** UV protection: four key requirements and influencing stakeholders.

in turn depend again on the technology, *i.e.* the form of the sunscreen must be appealing enough that it is used properly and frequently enough. Stakeholders may also play an important role. Conflicting messages from the various stakeholders, *e.g.* about nanotechnology, endocrine disruption or a possible vitamin D deficiency can cause confusion and insecurity among sunscreen users that can affect compliance. We think that the best measure to clarify these issues is information and education based on science. With this paper we also hope to contribute to this clarification process.

After elaborating on the notion of the "ideal sunscreen", we discuss the four requirements regarding where we stand on a qualitative ranking scale between poor and perfect and what still needs to be done to move towards perfection.

## The ideal sunscreen

The purpose of a sunscreen is the prevention of sunburn, photoaging, and ultimately skin cancer. In most cultures prevention of sunburn, the more or less directly perceivable effect of an overdose of solar radiation, is practised by sun avoidance, by seeking shade and covering up. In these forms of protection, solar radiation is more or less reduced uniformly—without preference for either UVB or UVA. During evolution human skin has adapted to the specific solar spectrum that reaches the Earth's surface.

With the introduction/invention of topical sunscreens, photoprotection became biased towards UVB, as it was the target of protecting human skin against the painful experience of sunburn. At that time the damaging effects of UVA radiation had not yet been recognized, and so UVA protection was not implemented in those products. This imbalance fostered the argument that extensive use of sunscreens may promote rather than prevent skin cancer,[2] as people were invited to stay longer in the sun without getting sunburned—however receiving high doses of unfiltered UVA radiation. As early as 1991, Diffey advocated uniform UV protection; this at a time when the importance of UVA in photoaging and skin cancer was not yet of general consideration.[3]

Over the years the evidence grew that UVA is not completely harmless after all. A review on ultraviolet A and melanoma suggests a potential role of UVA *via* the induction of reactive oxygen species, ROS, although it is still not fully conclusive.[4] The important role of UVA in photoaging and photocarcinogenesis is now better understood.[5,6] Nonetheless, not all sunscreens provide sufficient UVA protection.[7] We advocate that the "ideal sunscreen" should provide uniform UVB/UVA protection,[8] because this assures that the natural spectrum of sunlight is attenuated without altering its quality and thus being in harmony with evolution. New broad-spectrum sunscreens will eventually lead us back toward uniform UV protection that sun avoidance and covering-up had provided all along. Clothing is, in a way, the ideal sunscreen;[9,10] it offers practically uniform UVB/UVA protection, is water resistant and does not have to be reapplied; the Ultraviolet Protection Factor (UPF) remains constant as long the garment is worn. In general, even an UPF 5 T-shirt is good enough to prevent sunburn. Why is that? A major reason is that fabrics provide practically uniform UVB /UVA protection, so the UPF value is maintained in real sun. Furthermore, the UPF *in vitro* measurement is already calculated using spectral power of terrestrial sunlight, and not a UVB-biased solar simulator as is the case in SPF measurement. Finally, UPF 5 may be at least comparable with SPF 15 because in practical life people apply much less than the recommended 2 mg $cm^{-2}$ of the sunscreen, resulting in a realistic SPF of 5—about 1/3 of the labelled value. For patients with special UV or light sensitivity, UV protective clothing should be worn with labelled UPF up to 40 or higher.

## Four requirements for good UV protection—where we stand and what still needs be done

### 1. Technology

On the way to the ideal sunscreen, technology plays a key role. The goal is to reduce the amount of UV radiation that reaches the skin over a broad spectral range. UV filters are the heart of this technology, but also the formulation of the sunscreen is instrumental. The best UV filter combination cannot perform, *i.e.* spread uniformly and sustainably over the skin, if the sunscreen is formulated poorly. Fig. 2 shows that there are many "UVB filters" covering UVB (290–320 nm) and UVA II (320–340 nm), but now also UVA I (340–400 nm) filters and broad-spectrum UV filters that cover UVB, UVA II and UVA I are available as single molecules[11] except in the USA. Theoretically all the UV filter technology is thus available, but there are still a few reasons why it is or cannot be used everywhere by everyone.

There are four basic requirements for UV filters in order to be useful and used in sunscreens, *i.e.* (1) efficacy, (2) safety, (3) registration, (4) patent freedom (freedom to operate).[12] If one of them is not fulfilled a UV filter has no value for the sunscreen manufacturer, *e.g.* the modern broad-spectrum UV filters that are not yet approved by the US FDA cannot be incorporated in US sunscreens. We now assess the four basic requirements of the UV filters.

**1.1 Efficacy.** Fig. 3 illustrates with examples calculated on a sunscreen simulator[13] how sunscreens can be improved by the incorporation of modern broad-spectrum UV filters. The SPF 30 sunscreen "Yesterday" contains higher concentrations of UV filters than "Today" sunscreen for the same SPF and better UVA protection. By definition these two sunscreens protect equally well against laboratory-induced erythema under SPF testing conditions. However looking at the extinction or transmission spectra reveals that the "Today" sunscreen protects better against UVA radiation, mainly UVA I (340–400 nm). The "Today"

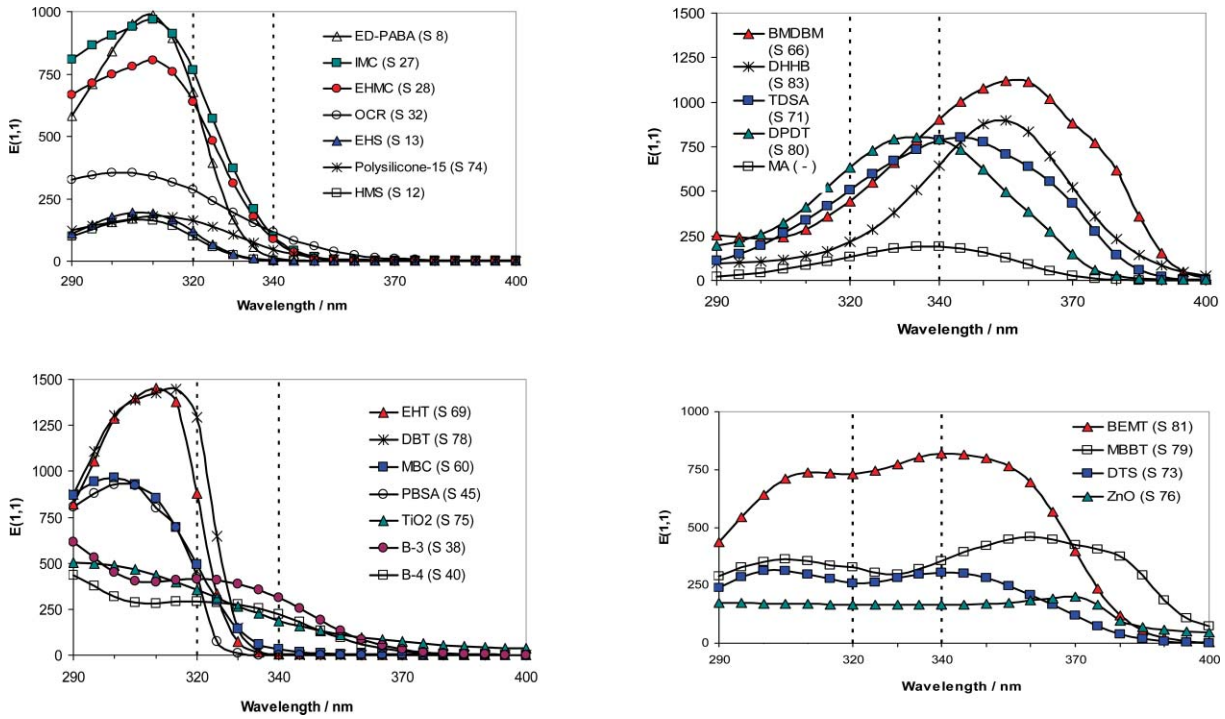



**Fig. 2** Available sunscreen actives (for UV filter identification and regulatory status, see Table 3).

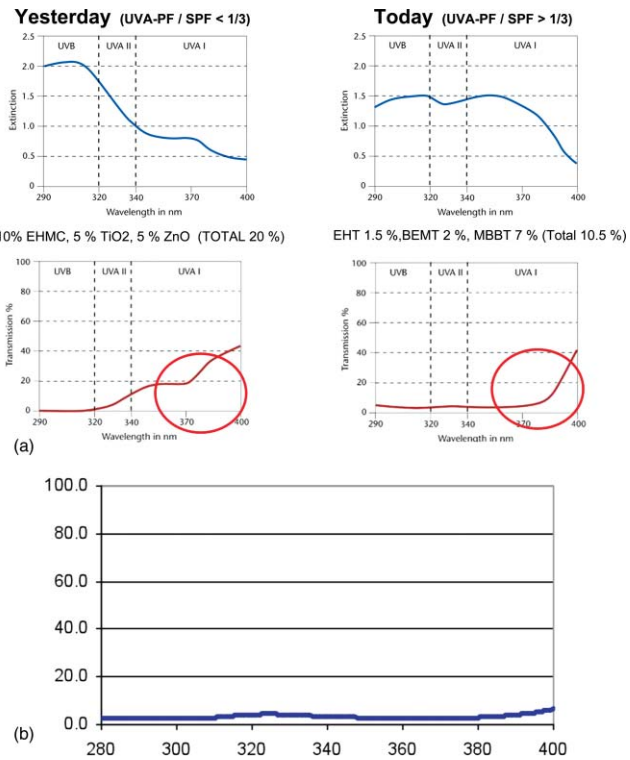



**Fig. 3** (a) UV protection profile "Yesterday" and "Today" (ref. sunscreen simulator). b White fabric (UPF 30) UV with practically uniform protection from 290 to 400 nm.

sunscreen is well on the way towards "ideal sun protection", as the comparison with the UV transmission curve of a white textile swatch treated with UV filter of UPF 30 shows (Fig. 3b).

Another important part of technology improvement is stabilizers for the photo-unstable UVA filter avobenzone (butylmethoxydibenzoylmethane, BMBM). With the help of other UV filters and triplet quenchers, avobenzone can be photostabilized considerably. Table 1 shows the most common UV filters and other ingredients used for this purpose.[14]

**1.2 Safety issues.** Modern sunscreen products should provide broad-spectrum UV protection and may contain one or several UV filters. A modern UV filter should be insensitive to changes in ambient temperature, photostable, water resistant, nontoxic, and easy to formulate. Identification of a substance that meets these criteria is as difficult as discovering a new drug; hundreds of new molecules are synthesized and screened before a lead candidate is identified. The most important aspect in the development of a new UV filter is its safety (Table 2). Skin penetration potential is measured *in vitro* using human skin or, when required by regulations, *in vivo* by tape stripping. Because

**Table 1** Stabilizing avobenzone (BMBM)

| % Stabilizer added | % Avobenzone remaining after 25 MEDs UV exposure |
|---|---|
| No stabilizer | 23% |
| Octocrylene, 3.6% | 90% |
| 4-Methylbenzilidine camphor, 5% (not USA) | 87% |
| Bemotrizinol, 5% (not USA) | 81% |
| Oxybenzone, 5% | 80% |
| Diethylhexyl syringylidenemalonate, 0.8% | 73% |
| Polysilicone-15, 4% (not USA) | 53% |
| Tris(tetramethylhydroxypiperidinol)citrate, 2% | 53% |
| Butyloctyl salicylate, 5% | 50% |
| Polyester-8, 3% | 50% |

**Table 2** Safety testing of new UV filters (EU requirements)

| | |
|---|---|
| Acute oral toxicity | Mutagenicity/genotoxicity |
| Acute dermal toxicity | Phototoxicity; photoallergenicity |
| Repeated dose oral toxicity | Photomutagenicity |
| Irritation (skin) | Safety evaluation |
| Irritation (mucous membranes) | Additional studies depending upon the results of the dermal absorption test and the outcome of the other studies |
| Sensitisation | |
| Dermal absorption | |
| Teratogenicity | |

modern sunscreens are also selected on the basis of their binding to the stratum corneum and are formulated as poorly penetrating emulsions, they generally have very low to negligible penetration rates.

The margin of safety of new UV filters for application to humans is estimated by comparing the potential human systemic exposure with the no-effect level from *in vivo* toxicity studies. Only substances with a safe toxicological profile and a margin of safety of at least 100-fold are approved for human use.[15] Modern sunscreens are safe for children and adults. Percutaneous penetration and irritation rates of topically applied substances are similar in children and adults. The dermal penetration of a UV filter is the "gate" through which systemic toxicity testing is routinely deemed necessary or unnecessary. There is no evidence that, regardless of particle size, inorganic UV filters, titanium dioxide and zinc oxide, penetrate beyond the stratum corneum of normal, undamaged skin. Whereas some organic sunscreens have been found to penetrate skin and have been measured in the blood and urine of human subjects, the systemic exposure is limited. A favourable human safety profile exists for commonly used organic and inorganic UV filters.

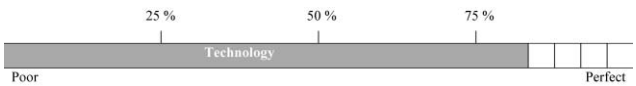
In conclusion, sunscreens are safe protective devices that have undergone stringent safety and efficacy evaluation.[16] It is hoped that demonstration of the safety of sunscreens positively influences their image in public and thus has a positive effect on compliance

**1.3 Registration.** The current status of the worldwide regulation of UV filters has recently been published by Ahmed.[17] UV filter regulations in nine major geographic markets—the U.S., Europe, Canada, Australia and New Zealand, China, Japan, South Africa, ASEAN (South-East Asia) and the MERCOSUR (South America)—are outlined. Ultraviolet (UV) filters are regulated globally as either over-the-counter (OTC) drugs, cosmetics, or quasi-drugs. All countries have a listing of permitted ultraviolet filters including maximum concentrations allowed in sunscreens or they follow a major world regulator or organization such as the Food and Drug Administration (FDA), Colipa (the European cosmetic trade association), or the Japan Cosmetic Industry Association (JCIA).

The registration status of the most popular UV filters is given in Table 3 for the most important regions. It is striking how few UVA or broad-spectrum UV filters are available in the USA. In 2007 the International Cooperation on Cosmetics Regulation (ICCR) was officially launched. ICCR is a formal dialogue between regulators and industry from the United States, Europe, Canada, and Japan to promote global harmonization of regulations for cosmetics and personal care products. Because regulations in different countries often conflict, increasing costs to manufacturers and straining government resources. The mission of ICCR is to identify ways to better align regulations and remove regulatory obstacles among the regions while maintaining the highest level of global consumer protection. Table 3 shows that there is still a long way to go towards global harmonization regarding registration.

**1.4. Patent freedom (freedom to operate)[12].** Patent freedom means the free use of sunscreen actives by any sunscreen manufacturer, *i.e.* without any uncertainty about whether any third party patent rights are infringed by the use of a particular ingredient. Thus, as soon as the identity of a new ingredient becomes known, its manufacturer/supplier has to make sure that "all" applications are disclosed in detail and explicitly as well, *e.g.* combinations of that novel ingredient with other sunscreen actives and other compounds such as emollients, emulsifiers, thickeners or stabilizers, otherwise such a new ingredient faces the threat of being blocked from major third party claims/applications. A classic example is the combination of the UV filters Bis-ethylhexyloxyphenol methoxyphenyltriazine (BEMT) and disodium phenyl dibenzimidazole tetrasulfonate (DPDT) which were approved in Europe 10 years ago. The combination of these two UV filters is still mutually blocked by the two leading sunscreen manufacturers in Europe and for everyone else in the countries where the patent applications were filed[12] and thus does not exist in the market. A strategy to avoid such situations is to publish all combinations of ingredients and claims with the new ingredient. Institutions to publish quickly now exist on the internet, *e.g.* www.ip.com. "IP-dot-com" enables innovative companies to quickly and easily protect their inventions by offering security services for many aspects of the invention process, from the safeguarding of sensitive information such as R&D lab notebooks to the rapid publication and creation of prior art in the form of technical disclosures.

**Conclusion/assessment (technology).** Due to the recent development of new UV filters that cover practically the whole range from UVB to UVA I (290–400 nm) we rank technology around 80% on the scale between poor and perfect. To come closer to perfection, global availability of the modern UVA I and broad-spectrum UV filters is required, *i.e.* mainly US registration. Furthermore, the safety of UV filters may have to be communicated better in order to convince all stakeholders and positively influence compliance. The ultimate confirmation that technology is on the right track would be evidence that sunscreens can help prevent melanoma. Diffey already suggested this in a recent paper "Sunscreens and melanoma: the future looks bright".[18]




## 2. Assessment/measurement

The Sun Protection Factor (SPF) is a well established direct measure of the sunscreen protection against erythema caused by solar-simulated sun-light, but is not *a priori* sufficient as a measure against photo-aging and skin cancer. For adverse effects other than sunburn the protection against UVA radiation should also be assessed. Methods to assess the performance of a sunscreen regarding SPF and UVA protection are instrumental in achieving good UV protection. There are two dimensions in the assessment,

**Table 3** Cross-reference list of all UV filters used in the BASF sunscreen simulator (www.basf.com/sunscreen-simulator)

| INCI | COLIPA | USAN | Trademark | Abbreviation | Incorporation Limits (%) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Australia | Europe | Japan | USA |
| Broad-spectrum and UVA I (340–400 nm) | | | | | | | | |
| Bis-ethylhexyloxyphenol methoxyphenyl triazine | S81 | Bemotrizinol | Tinosorb S | BEMT | 10 | 10 | 3 | [a] |
| Butyl methoxydibenz olymethane | S66 | Avobenzone | Parsol 1789 | BMBM | 5 | 5 | 10 | 3 |
| Diethylamino hydroxybenzoyl hexyl benzoate | S83 | | Uvinul A Plus | DHHB | 10 | 10 | 10 | — |
| Disodium phenyl di benzimidazole tetrasulfonate | S80 | Bisdisulizole disodium | Neo Heliopan AP | DPDT | 10 | 10 | — | — |
| Drometrizole trisiloxane | S73 | — | Mexoryl XL | DTS | 15 | 15 | — | — |
| Menthyl anthranilate | — | Meradimate | | MA | 5 | — | — | — |
| Methylene bis-benzotriazolyl tetramethylbutylphenol | S79 | Bisoctrizole | Tinosorb M (active) | MBBT | 10 | 10 | 10 | [a] |
| Terephthalylidene dicamphor sulfonic acid | S71 | Ecamsule | Mexoryl SX | TDSA | 10 | 10 | 10 | [ab] |
| Zinc oxide | S76 | Zinc oxide | ZnO (Nanox) | ZnO | No limit | [c] | No limit | 25 |
| UVB (290–320 nm) and UV all (320–340 nm) | | | | | | | | |
| 4-Methylbenzylidene camphor | S60 | Enzacamene | Eusolex 6300 | MBC | 4 | 4 | — | [a] |
| Benzophenone-3 | S38 | Oxybenzone | Uvinul M40 | BP3 | 10 | 10 | 5 | 6 |
| Benzophenone-4 | S40 | Sulisobenzone | Uvinul MS40 | BP4 | 10 | 5 | 10 | 10 |
| Polysilicone-15 | S74 | — | Parsol SLX | PS15 | 10 | 10 | 10 | — |
| Diethylhexyl butamido triazone | S78 | — | Uvasorb HEB | DBT | — | 10 | 5 | [a] |
| Ethylhexyl dimethyl PABA | S8 | Padimate O | Eusolex 6007 | EHDP | 8 | 8[d] | 10 | 8 |
| Ethylhexyl methoxycinnamate | S28 | Octinoxate | Uvinul MC 80 | EHMC | 10 | 10 | 20 | 7.5 |
| Ethylhexyl salicylate | S13 | Octisalate | Neo Heliopan OS | EHS | 5 | 5 | 10 | 5 |
| Ethylhexyl triazone | S69 | Octyltriazone | Uvinul T 150 | EHT | 5 | 5 | 3 | [a] |
| Homomenthyl salicylate | S12 | Homosalate | Eusolex HMS | HMS | 15 | 10 | 10 | 15 |
| Isoamyl p-methoxycinnamate | S27 | Amiloxate | Neo Heliopan E 1000 | IMC | 10 | 10 | — | [a] |
| Octocrylene | S32 | Octocrylene | Uvinul N 539 T | OCR | 10 | 10 | 10 | 10 |
| Phenylbenzimidazole sulfonic acid | S45 | Ensulizole | Eusolex 232 | PBSA | 4 | 8 | 3 | 4 |
| Titanium dioxide | S75 | Titanium dioxide | Eusolex T2000 | $TiO_2$ | 25 | 25 | No limit | 25 |

[a] Time and extent application (TEA), proposed rule on FDA approval expected 2009. [b] Approved in certain formulations up to 3% *via* New Drug Application (NDA) route. [c] Currently under SCCP review, non-nano grade approved. [d] Not supported in the EU and may be delisted.

*i.e.* the magnitude (quantity) and the breadth (quality) of the protection spectrum. *In vivo* methods exist for both the SPF and the UVA Protection Factor (UVA-PF). Various *in vitro* methods exist for the assessment of UVA protection (Table 4), but not yet for the SPF. A variation of the *in vitro* methods is the so-called *in silico* method. It allows the calculation of SPF as well as all the UVA indices.[19] The *in silico* calculation based on the absorption spectrum measured for each UV filter individually and an assumption about the irregular sunscreen film on the skin is very useful in the development phase of sunscreens. It also helps in understanding sunscreens, *e.g.* it can be used to determine how the SPF is affected by applying smaller amounts than the 2 mg $cm^{-2}$ used in SPF testing. More details are discussed in ref. 20.

**2.1 SPF measurement (*in vivo*).** The SPF measured *in vivo* on the back of volunteers is the gold standard for the assessment of sunscreens. The erythema endpoint is of biological relevance and for a long time erythema prevention has been the prime objective of wearing sunscreen. In the following we show that the current SPF measurement requires improvement. For historical and technical reasons the UV source for SPF testing is UVB biased compared to the sun spectrum (CIE). Fig. 4a shows that there is about a factor 2 difference in UVB output where UV is most erythemogenic (300–320 nm, Fig. 4b). On the other hand the artificial sun is filtered in the UVA I part towards 400 nm where the energy of the

**Table 4** Overview of UVA assessment methods

| Type of method | | |
|---|---|---|
| ***In vivo*** | Persistent pigment darkening (PPD) standard in Asia, Europe and USA | JCIA Standard (Jap.), AFS APS Standard (F), US-FDA proposed rule |
| ***In vitro*** | **UVA/UVB ratio** | **Diffey *et al.*, Boots, 1994, 2008** |
| | Critical wavelength | Diffey *et al.*, 1994 |
| | Australian standard | AS/NZS 2604, 1998 |
| | UVA-Balance (DIN 67502) | Task force of German Cosmetic Society, DGK, 2005 |
| | **UVA-PF (PPD)** | **EC standard, COLIPA guideline 2007** |
| | **UVA1/UV ratio** | **US-FDA proposed rule 2007** |
| | **Spectral Uniformity Index** | **Diffey, 2009** |
| ***In silico*** | Computer simulation based on spectral data and skin model (*e.g.* step-film model) | Herzog *et al.*, 2002 Ciba® Sunscreen Simulator Ferrero *et al.*, 2003 |



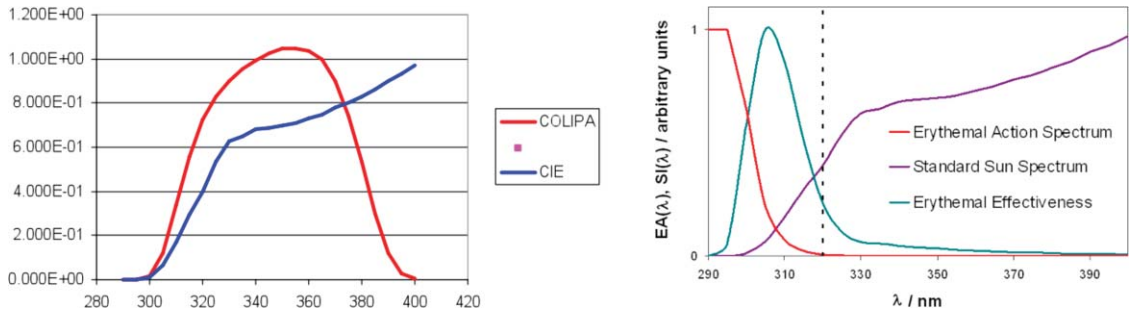



**Fig. 4** Different sun spectra, COLIPA and CIE.



sun is highest. This has consequences for the measurement of the SPF. The use of a UVB-biased lamp overestimates the SPF of a sunscreen with a UVB-biased protection profile, but on the other hand is able to predict "the real SPF" in natural sunlight for true broad-spectrum sunscreens since the latter protects uniformly and thus it does not matter at which wavelength this protection level is measured.

In a human *in vivo* study, Young *et al.* showed that a sunscreen's labelled SPF may overestimate protection at temperate latitudes, especially when the protection profile of the sunscreen is UVB biased, *i.e.* the SPF depends on the spectrum (*e.g.* latitude) and the sunscreen protection profile.[21] With the help of the sunscreen simulator we show the influence of the protection profile of a sunscreen and the sun spectrum on the SPF of a sunscreen.

Another way to improve SPF *in vivo* measurement by using only a single exposure on sun-protected skin (instead of five or seven exposures) has been proposed by Diffey.[22] The method is supposed to yield an estimate of a product's mean SPF that is comparable or better in accuracy to estimates obtained by conventional multi-exposure testing.

**2.2 SPF *in vitro* and *in silico* measurement.** At the moment there exists no reliable SPF *in vitro* method. One of the major problems is the substrate which should act as a surrogate for the skin surface. PMMA plates with a roughness of 6 or 16 μm are presently favoured, but do not yet yield satisfactory results. A variation of the *in vitro* assessment of a sunscreen is the *in silico* calculation. In our experience *in silico* calculations are more reliable than *in vitro* at the moment. *In silico* does of course also go back to *in vitro* measurement of the extinctions of the individual UV filter, but uses an algorithm to account for the irregular sunscreen film on the skin and also for photoinstabilities. *In silico* are by definition reproducible. The sunscreen simulator is freely accessible for the determination of SPF and UVA indices at www.basf.com/sunscreen-simulator. The accuracy is based on model parameter adjustments on *in vivo* results (sunscreen reference samples). The *in silico* calculation uses "the correct" irradiation approach to account for photoinstability which leads to the "integrated absorbance spectrum".[23] This corresponds to the *in vivo* situation where the endpoint is reached when a dose of 1 MED has been transmitted through the sunscreen onto the skin. The various *in vitro* UVA methods (Boots, COLIPA, FDA) all use different doses of pre-irradiation that are somewhat arbitrary.

Furthermore *in silico* bottom up calculation takes into account a model of the irregular sunscreen film on the skin, photostability of UV filter combinations, distribution of UV filters in oil and aqueous phases, as well as boosters and stabilizers.

The sunscreen simulator program can be used to determine how the SPF is affected by applying smaller amounts of sunscreen. There is a lot of confusion how the SPF will vary with the amount applied. This is especially important to know because we know that people normally apply far less sunscreen than used in sunscreen testing, *i.e.* around 1 mg $cm^{-2}$ or less rather than 2 mg $cm^{-2}$. Furthermore sunscreens are, of course, used to protect against the real sun and not the simulated sun used in SPF testing. We can therefore compare SPFs at various amounts applied (0.5–3 mg $cm^{-2}$) under solar-simulated sun conditions and under "real sun"[24] conditions (Fig. 5) (CIE sun). In the *in silico* experiments, a UVB-biased sunscreen and a broad-spectrum sunscreen were used to see the influence of the protection profile (Table 5).

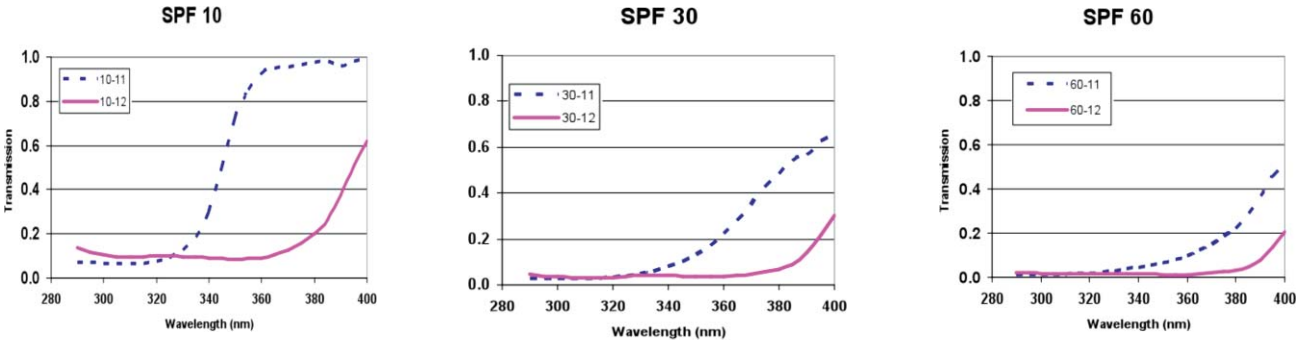
Contrary to general belief, the relationship between SPF and amount applied is quasi-linear. Only with very high UVA protection at very high SPF (50+, 60) does the relationship move towards quasi-exponential. Looking at sunscreen compositions with different degrees of UVA protection, but adjusted for the same SPF at an application amount between 0.5 and 3.0 mg $cm^{-2}$, the calculations with the irradiance spectrum of solar-simulated light used in SPF testing show practically no difference between the UVB-biased sunscreen and the broad-spectrum sunscreen (Fig. 5a, SSS: solar-simulated sun). However, the difference becomes relevant under the CIE "real sun" conditions (Fig. 5b). Under the "real sun" the SPF values are all lower than measured under laboratory conditions, but the reduction for the broad-spectrum sunscreen is minimal (*e.g.* −6%) and for the UVB-biased substantial (*e.g.* −25%). The ideal sunscreen with a flat spectrum would not show any difference.

In conclusion, it is shown that the accuracy and robustness of the SPF and other protection factors will improve significantly with the availability of true broad-spectrum sunscreens because uniform protection profiles lead to protection independent of the action spectrum of the endpoint and of the UV-radiation source, especially under "real-sun" conditions.

**2.3. UVA measurement (*in vivo* and *in vitro*).** Both UVA *in vivo* and *in vitro* methods are available.[25–29] Persistent Pigment Darkening [(PPD), *in vivo*] is somewhat similar to SPF, but is a questionable biological endpoint and certainly not as relevant as erythema. Regarding the specifications of the UV source for the *in vivo* measurement we face a similar problem as in the SPF method. The spectrum in the laboratory setup is different to the real sun. Sayre and Dowdy point out that the relative lack of UVA-I compared to sunlight (340–400 nm) radiation in the

**Table 5** Compositions of UVB-biased and broad-spectrum sunscreen used in *in silico* experiment

| SPF 10 (SSS) | | | | SPF 30 (SSS) | | | | SPF 60 (SSS) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| UVB sunscreen | | Broad-spectrum | | UVB sunscreen | | Broad-spectrum | | UVB sunscreen | | Broad-spectrum | |
| SPF | UVA-PF | SPF | UVA-PF | SPF | UVA-PF | SPF | UVA-PF | SPF | UVA-PF | SPF | UVA-PF |
| 10-11 | 10-11 | 10-12 | 10-12 | 30-11 | 30-11 | 30-12 | 30-12 | 60-11 | 60-11 | 60-12 | 60-12 |
| EHMC | 9% | BEMT | 2% | EHMC | 7.5% | EHT | 1.0 | PBSA | 4 | PBSA | 2.5 |
| | | MBBT | 1.60% | HMS | 10.0% | BEMT | 3.0 | EHS | 5 | EHMC | 1 |
| | | | | $TiO_2$ | 3.0% | MBBT | 6.0 | HMS | 8 | MBBT | 7 |
| | | | | B-3 | 5.0% | | | OCR | 1 | BEMT | 4 |
| | | | | | | | | $TiO_2$ oil | 1 | DHHB | 7 |
| | | | | | | | | $TiO_2$ aq | 4 | | |
| | | | | | | | | B-3 | 6 | | |
| | | | | | | | | BMBM | 3 | | |
| **Total** | **9%** | | **4%** | | **25.5%** | | **10.0** | | **34** | | **21.5** |



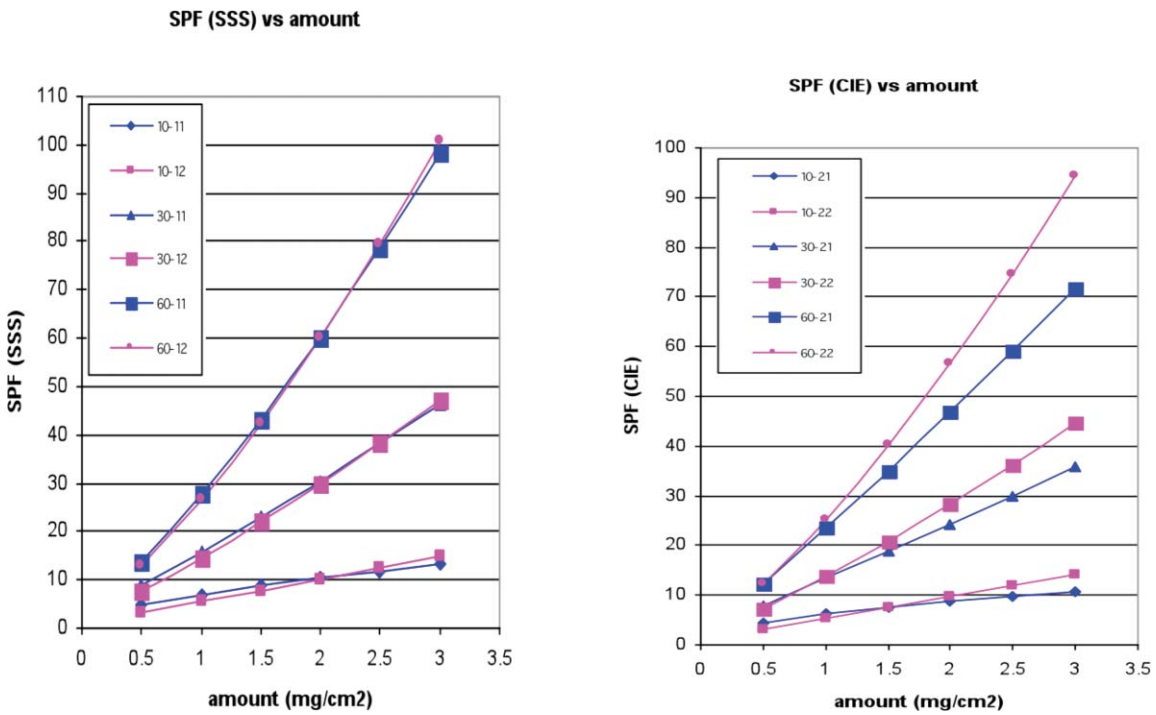




**Fig. 5** (left) SPF *vs.* amount applied (SSS). (right) SPF *vs.* amount applied (CIE).

current JCIA UVA solar simulator specification allows the method to generate higher UVA protection factors than sunscreens will provide in sunlight.[30] However, contrary to the SPF, there are valid alternative UVA *in vitro* methods, by relative assessment of breadth of protection, *e.g.* ratios such as UVA-PF/SPF, UVA/UVB or UVA I/UV. This internal normalization makes the index more robust than an absolute measure that is required for an SPF (*e.g.* less dependent on the substrate). In fact there is no need for an extra *in vivo* UVA measurement; the *in vitro* methods cover the whole UVA I range up to 400 nm.

**Table 6** European Commission recommendation (22 Sept 2006)

| Labeled category | Labeled Sun Protection Factor | Measured Sun Protection Factor | Recommended minimum UVA Protection Factor | Recommended minimum critical wavelength |
|---|---|---|---|---|
| Low protection | 6 | 6–9.9 | 1/3 of labeled SPF (*e.g.* >20 @ SPF 50+) | 370 nm |
| | 10 | 10–4.9 | | |
| Medium protection | 15 | 15–19.9 | | |
| | 20 | 20–24.9 | | |
| | 25 | 25–29.9 | | |
| High protection | 30 | 30–49.9 | | |
| | 50 | 50–59.9 | | |
| Very high protection | 50+ | ≥60 | | |



The available *in vitro* UVA methods take into account possible photo-instabilities of sunscreens by an irradiation step. The applied irradiation doses are, however, different (COLIPA, Boots, FDA). A potential solution is again applying the integrated spectrum approach, *i.e.* the result of a total dose that transmits one minimal erythema dose (1 MED) through the sunscreen, as is the case in the *in vivo* SPF measurement. Once an *in vitro* SPF method becomes available, this UVA problem will be resolved automatically. In the meantime the integrated spectrum approach may already be used for UVA *in vitro* measurement, *i.e.* all UVA indices can be derived from the integrated absorbance spectrum. Efforts are currently underway at ISO (International Organization for Standardization) to harmonize worldwide SPF and UVA testing standards.[31–33] The ISO emphasis is on finding *in vitro* methods to eventually replace the invasive *in vitro* methods.

The major drawback of *in vitro* methods can be summarized in the phrase "skin is not plastic". So it is indeed questionable if it will ever be possible to replace human involvement in sunscreen testing. A possible approach may be diffuse reflectance spectroscopy (DRS). DRS is applied on human skin but non-invasive without irradiation.[34] Accurate results can only be achieved in the UVA region, but photostability could also be assessed even *in vivo* under real conditions. The authors found a positive relationship (regression coefficient $r^2 = 0.90$) of PFA values between *in vitro* PFA testing and the *in vivo* DRS testing. There was also a very good correlation (regression coefficient $r^2 = 0.99$) between the *in vivo* PFA/PPD values and UVA protection factor obtained from the DRS method. Conclusion: DRS is a fast method, non-invasive and does not involve any subject irradiation, except some minimal dose that is required to measure the diffuse reflectance spectrum The technique is a good estimator for the *in vivo* UVA protection factor as well as a way to assess, *in vivo*, the photostability of sunscreen formulation in the UVA.

**Conclusion/assessment (assessment/measurement).** Although SPF is well established and there are numerous UVA assessment methods. We rate the status of sunscreen assessment and measurement only around 50% on the poor-to-perfect scale. There is still a very long way to go until we have reliable realistic methods, hopefully without the need to burn human volunteers.


## 3. Norms and standards

The level and quality set by norms and standards is also crucial for good UV protection. This can happen by authorities but is normally pioneered by the industry. There is now more or less world wide consensus about what SPF corresponds to the low, medium, high or highest protection category and about capping SPF at 50+, except for the USA due to the lack of a final rule from the FDA. The overzealous three digit SPFs were first encountered in Japan and Europe over ten years ago. After settling at SPF 50+ about five years ago, the race began in the USA, reaching the magic 100+ in the summer of 2009. It seems very likely that this race will also end soon in the USA when the FDA rectifies the final ruling.[35]

For UVA protection, the development of categories or pass/fail criteria is still in debate. UVA standards are well established in Australia,[36] the United Kingdom[37] and Japan.[26] Only recently the European Commission released a UVA recommendation[38] and the US Food and Drug Administration a proposed rule.[35] Table 6 shows the EC recommendation released in 2006 with four levels of protection and only a total of eight distinct numbers for the SPF labeling (6, 10, 15, 20, 25, 30, 50 and 50+). The intention is to reduce and simplify labeling. This rule is sensible in view of the difficulties of higher SPF sunscreens regarding measurement, reliability and compliance.

UVA protection in Europe is handled in a pass/fail fashion. The SPF is recognized as the leading indicator for UV protection (quantity) to which a certain UVA protection has to be adapted. The simple criterion is that the UVA-PF (measured *in vivo* or *in vitro*) has to be equal to or greater than 1/3 SPF. This means that a sunscreen labeled SPF 50+, *i.e.* measure SPF >60 has to have a UVA-PF greater than 20. This is well on the way towards "the ideal sunscreen" with uniform UVB/UVA protection. However, it is important to understand that the ratio of UVA-PF to SPF is dependant on the application thickness. So a particular ratio obtained under laboratory conditions at 2 mg $cm^{-2}$ will change under normal usage when consumers typically apply about one-half this thickness. At the lower application rate the UVA-PF will decline less than the SPF and thus the UVA-PF/SPF ratio will be higher at lower application rate.[11] This may also happen to a lower extent with indices based on absorbance (*e.g.* Boots Star ratio, Spectral Uniformity Index).

Although the variety of standards and labelling is confusing, there is a common trend towards more uniform UV protection. It started modestly with the pioneers in Japan and Australia. Since then the global situation has been constantly improving

**Table 7** Global development of norms and standards

| | AUS | JAP | EU | UK | USA |
|---|---|---|---|---|---|
| SPF (*in vivo*) | AS/NZS | International harmonized SPF method | International harmonized SPF method | International harmonized SPF method | FDA |
| Cap | SPF 30+ | SPF 50+ | | | SPF 50+ |
| UVA (year) | AS/NZS (1983, 1998) | JCIA (1995) | EC Recomm. (2006) | Boots (1992, 2008) | FDA (2007) |
| *In vivo* | — | PPD | PPD | — | PPD |
| *In vitro* | Transmission (320–360 nm) < 10% | — | UVAPF/SPF > 0.33, CW > 370nm | UVA/UVB > 0.9 (max. 5 stars) | UVAI/UV > 0.95 (max. 4 stars) |
| UVA symbol | None (pass/fail) | PA+, PA++, PA+++ | UVA | UVA ULTRA | ★★★★ Highest |
| Trend | → Towards ideal sun protection! → | | | | |

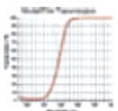
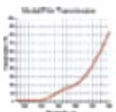
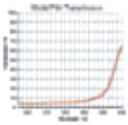
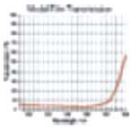
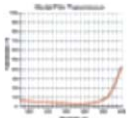
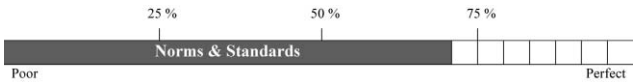
| SPF 20 Sample | A | B | C | D | E |
|---|---|---|---|---|---|
| Transmission -profile (Sunscreen-Simulator) |  |  |  |  |  |
| UVA-PF | 1·1 | 3·9 | 10·9 | 16·3 | 20·7 |
| Japanese UVA-rating | None | PA+ | PA+++ | PA+++ | PA+++ |
| European UVA-rating | None | None | UVA | UVA | UVA |
| Proposed US UVA-rating | No UVA Protection | ★★☆☆ Medium | ★★★☆ High | ★★★☆ High | ★★★★ Highest |
| (UVAI/UV) | (0·05) | (0·64) | (0·83) | (0·92) | (0·95) |

**Fig. 6** Evolution of UVA protection in sunscreens of SPF 20.

(Table 7). The European recommendation surpassed the pioneering standards from Japan and marks an important step towards the ideal sunscreen with uniform UVB /UVA protection. The highest four and five star categories by the Boots 'ultra' and FDA 'highest' category already come very close to the ideal sunscreens. They allow sunscreen manufacturers to differentiate their superior products and are thus important for the further development of sunscreens.

Fig. 6 shows the evolution of the protection profile of commercial SPF 20 sunscreens A–D, all purchased in 2008 in Europe and an experimental sunscreen E[39] that would fall into the highest UVA protection class in the FDA Proposed Rule. This series of sunscreen shows that there is more or less agreement worldwide over what the minimum requirement for UVA protection should be, *i.e.* UVA-PF equal or greater than 1/3 SPF, PA+++ or three stars in the Boots and FDA system.

**Conclusion/assessment (standards and norms).** The importance of norms or standards is well documented in the evolution of UVA protection. We rate the status of norms and standards about 2/3 between poor and perfection. A lot has already been achieved in parts of the world and we know how it should be, but there is still a long way towards global harmonization.




## 4. Compliance

The best sunscreen provides insufficient protection if not applied correctly, such as non-uniform application and inadequate amount or not at all. Compliance is the most important key factor for good UV protection. The other three factors discussed above all influence compliance. Technology affects the interaction of the components of the sunscreen with the skin and thus the homogeneous distribution of the UV filters on the skin's surface and influences the consumer's choice. If the formulation is not pleasant, the user will be less likely to reuse the product. Understanding sunscreens and the way the SPF is measured and

communicated also increases the credibility of sunscreens. Lack of compliance has many reasons. For the discussion we divide them into (1) technological reasons, (2) understanding of sunscreens, (3) mixed messages from stakeholders and (4) lack of awareness.

**4.1. Technological reasons.** The technical reason for lack of compliance falls into the category "efficacy" as part of the four basic requirements of UV filters discussed before. A sunscreen must be cosmetically elegant and pleasing in order to be applied correctly and frequently.

**4.2 Lack of understanding of sunscreens.** There are a few common misunderstandings about sunscreens that add to the confusion. A popular misconception is that an SPF 60 sunscreen is not twice as effective as an SPF 30 sunscreen (in preventing sunburn under laboratory conditions, we have to add). The argument is that an SPF 30 sunscreen absorbs 96.7% of the erythemogenic UV rays, whereas an SPF 60 sunscreen absorbs 98.3%, *i.e.* only 1.6% more. Fig. 7 shows the situation. The argument is correct regarding how much erythemogenic UVR is filtered out. However, what matters is not the amount filtered out but the amount of UVR transmitted onto the skin. Half as much erythemogenic UVR will reach the skin through an SPF 60 (labelled 50+) sunscreen than with an SPF 30 one; *i.e.* there is a factor 2 difference!

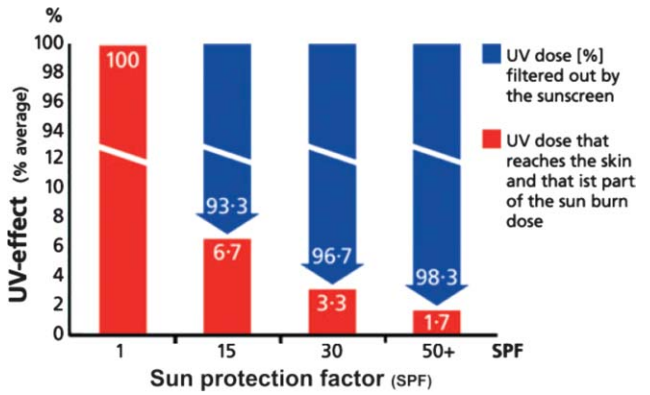



**Fig. 7** Understanding SPF 60 sunscreens provide double the protection as SPF 30.

Another topic of discussion is the SPF *vs.* amount applied. On pseudo-theoretical grounds, it is often argued that the relationship is always exponential, *i.e.* slapping on 1 mg $cm^{-2}$ instead of 2 mg $cm^{-2}$ of an SPF 25 sunscreen will result in an actual SPF of only 5. Clinical ring studies however showed that the relationship is fortunately much more favourable, *i.e.* quasi-linear. Hence the SPF 25 sunscreen is likely to still provide an actual SPF 12 if half the amount is applied as specified under test conditions. With the help of the sunscreen simulator we can calculate and understand the phenomenon that the relationship between thickness of a (non-uniform!) sunscreen layer and the SPF is quasi-linear for most sunscreens because of opposing influence (Fig. 5).

**4.3 Mixed messages by stakeholders.** Since sun protection is a health issue, there are regularly controversies in the media about the safety of the sunscreens and particularly their actives, the UV absorbers. A classic sunscreen issue is the compliance and misuse to extend sun exposure excessively.[40] It is argued that sunscreen use may even promote skin cancer rather than prevent it. This may actually have been true with the classic UVB-biased sunscreens. Autier now proposes the use of individual dosimeters in addition to sunscreen in order to limit the time of sun exposure to the time sunburn would occur without sunscreen.[41] For skin phototypes 1 or 2, the time to attain sunburn is short, maximum 10–20 min under full summer sun. With the modern broad-spectrum sunscreens available today this should now be a notion of the past. Diffey on the other hand advocates, based on the improvement of sunscreens in UVA protection, applying sunscreens as a preventative measure against melanoma according to the precautionary principle rather than waiting until clinical evidence becomes available.[42] In fact, it is not likely that there will ever be hard clinical evidence of melanoma prevention in the form of long duration double-blind studies.

**4.4 Lack of awareness.** The awareness of the public is mainly influenced by advertising of the sunscreen manufacturers, awareness campaigns of health organizations and the sunscreen issues discussed in the media. This is of course a very mixed bag of messages that pours onto the public. Wang and Halpern[43] give the following advice to increase awareness among the public:

– A successful public health message must be consistent and straightforward, easy to understand and simple to repeat.

– There are two major motivating factors in a photoprotection campaign: health-based (focusing on skin cancers), and appearance-based (focusing on photoaging); each appeals to different demographics.

– The message for photoprotection is: sun avoidance, seeking shade, and the use of protective clothing, hat and sunscreens.

– National and state governments should play a more active role in creating favourable legislative policies, while the fashion and beauty industries should be recruited to change public perception on the perceived attractiveness associated with tanned skin.

Sinclaire and Foley[44] report that social marketing campaigns to raise awareness of skin cancer prevention in Australia were successful even in reducing melanoma rates, but emphasize that long term investment in this area is required otherwise any population gains in behaviour are very likely to be quickly eroded.

**Conclusion/assessment (compliance).** For all the reasons discussed above, compliance is the least fulfilled requirement for good UV protection. We rate it at 30% on the poor-to-perfection scale. Compliance is the weakest element in the UV protection chain. Much needs to be improved. The contribution of the industry and all other stakeholders could be to provide a consensus of understanding on sound scientific grounds of sunscreens and their role among other UV protection measures.


## Summary

The ideal sunscreen provides uniform UVB/UVA protection because this assures that the natural sun spectrum is attenuated without altering its quality. Current sunscreen technology approaches the ideal goal of uniform protection. We have identified and assessed four key parameters for good UV protection (Fig. 8).

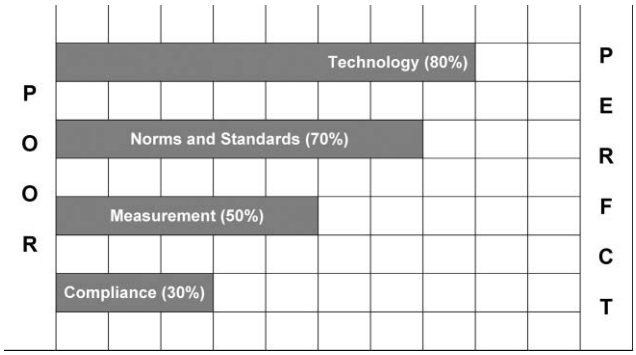



**Fig. 8** Assessment/ranking of key parameters in UV protection between poor and perfect (qualitative 2009).

In our assessment, product technology is closest to reaching the ideal goal (80%), whereas compliance ranks poor (30%). There is still room for improvement in SPF and UVA protection measurement, whereas the norms and standards help to increase the protection considerably, even when a standard level is not yet official, *e.g.* the proposed UVA rule in the USA that was published in 2007 has been followed by an increase of UVA protection. Fulfilling the four requirements discussed above moves topical protection products closer to being a reliable means of sun protection similar to sun avoidance and covering up by textiles. This will help understanding and resolving current issues around sunscreens and thus help improving compliance.

## Abbreviations

| | |
|---|---|
| CIE | International Illumination Committee |
| DRS | Diffuse reflectance spectroscopy |
| MED | Minimal erythema dose |
| PPD | Persistent pigment darkening |
| RSF | Radical skin/sun protection factor |
| SPF | Sun protection factor |
| SSS | Solar-simulated sun |
| UPF | Ultraviolet protection factor |
| UVA I | UVR in 400–340 nm range |
| UVA II | UVR in 340–320 nm range |
| UVB | UVR in 320–280 nm range |
| UVA-PF | UVA protection factor |
| UVR | Ultraviolet radiation |

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