Ultraviolet radiation and the skin: Photobiology and sunscreen photoprotection

Antony R. Young, PhD,[a] Joël Claveau, MD,[b] and Ana Beatris Rossi, MD[c,d]
London, United Kingdom; Québec City, Québec, Canada; and Toulouse, France

The efficacy of sunscreens can be measured by different methods, involving in vitro, ex vivo, or in vivo techniques. There is a need for a worldwide standardization of these methods to avoid misunderstanding and confusion among sunscreen users. The clinical benefits of sunscreens have been demonstrated in randomized controlled trials that established the role of sunscreens in the prevention of actinic keratoses, squamous cell carcinomas, nevi, and melanomas. Sunscreens also prevent photoimmunosuppression and signs of photoaging. Continued efforts in public education on the proper application of sunscreens and the practice of photoprotection in general are needed. (J Am Acad Dermatol 2017;76:S100-9.)

Key words: cyclobutane pyrimidine dimer; DNA photodamage; photoaging; photoimmunosuppression; pyrimidine(6-4)pyrimidone; skin cancer; sunscreen; ultraviolet radiation.

Terrestrial solar ultraviolet (UV) radiation (UVR) (~295-400 nm) comprises UVA (320-400 nm) and UVB (280-320 nm).[1] UVC (100-280 nm) does not reach the Earth's surface because it is completely absorbed by stratospheric ozone. UVB accounts for no more than about 5% of terrestrial UVR, but its effects are typically much greater than those of UVA. The intensity of UVB peaks at around midday, whereas that of UVA remains fairly consistent throughout the day. The clinical effects of UVR on normal-appearing human skin, which are mostly adverse, may be acute or chronic. The acute effects include erythema (sunburn), pigmentation (tanning), suppression of acquired immunity, and enhancement of innate immunity, all mostly caused by UVB,[2] and reduction of blood pressure by UVA[3,4] (Table I). Chronic effects include photocarcinogenesis and photoaging.[5] All effects are underpinned by molecular or cellular effects such as DNA damage, the generation of reactive oxygen species (singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals, and peroxynitrite), melanogenesis, apoptosis,

Abbreviations used:

AK:	actinic keratosis
BCC:	basal cell carcinoma
CPD:	cyclobutane pyrimidine dimer
FDA:	Food and Drug Administration
ISO:	International Standards Organization
KC:	keratinocyte cancer
MED:	minimal erythemal dose
MMP:	matrix metalloproteinase
SCC:	squamous cell carcinoma
SED:	standard erythemal dose
SPF:	sun-protection factor
UV:	ultraviolet
UVR:	ultraviolet radiation

From the St John's Institute of Dermatology, King's College London[a]; Department of Dermatology, Melanoma and Skin Cancer Clinic, Centre Hospitalier Universitaire de Québec—Hôpital Hôtel-Dieu[b]; Clinical Skin Research and Development Center, Pierre Fabre Dermo-Cosmétique, Toulouse[c]; and Department of Dermatology, Toulouse University Hospital.[d]

Publication of this supplement is supported by Laboratoires Dermatologiques Avène.

Disclosure: Dr Young discloses research funding and honoraria from Pierre Fabre Dermo-Cosmétique, and research funding from BASF and Walgreens Boots Alliance (manufacturers of sunscreen filters and sunscreen products, respectively). Dr Claveau discloses that he is a consultant and speaker for L'Oréal and a speaker for Bioderma Laboratoire Dermatologique, Johnson & Johnson, and Pierre-Fabre Dermo-Cosmétique. Dr Ana Beatris Rossi is a full-time employee of Pierre Fabre Dermo-Cosmétique.

Accepted for publication September 24, 2016.

Reprint requests: Antony R. Young, PhD, St John's Institute of Dermatology, Tower Wing (ninth floor), Guy's Hospital, Great Maze Pond, London SE1 9RT, UK. E-mail: antony.young@kcl.ac.uk.

Published online December 27, 2016.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2016.09.038

depletion of Langerhans cells, and expression of many genes and related proteins. The only widely established benefit of UVR in the skin is the photosynthesis of vitamin D that is initiated by the UVB-induced conversion of epidermal 7-dehydrocholesterol into previtamin D_3.

PHOTOBIOLOGY

UVR sensitivity

Skin phototype, as described by the Fitzpatrick scale,[6] is among the most useful clinical determinants of UVR sensitivity. Lower number skin types are more susceptible to sunburn, tanning ability is poor, and skin cancer risk is higher (Table II).

Personal UVR sensitivity can be measured by visual assessment of the minimal erythemal dose (MED), which is the amount of UVR needed to induce just perceptible erythema after exposure (typically 24 hours). In general, the MED increases with Fitzpatrick skin type, but there is considerable overlap between skin types, so MED may not be consistently predictive of skin type.[7] The MED is widely used in experimental photobiology, phototherapy, and calculation of a sunscreen's sun-protection factor (SPF).

An action spectrum is defined as a plot of wavelength versus the reciprocal of the dose required for a given photobiological outcome (usually expressed on a log scale), such as erythema. Most international organizations have adopted the action spectrum proposed by McKinlay and Diffey[8] in 1987, including the Commission Internationale de l'Eclairage.[9,10] Using this schema as a weighting function for solar UVR shows that, when the sun is high, over 80% of the erythemal response of the skin is a result of the 5% or less UVB in solar UVR. The erythema action spectrum is also used as the biological weighting function for the standard erythemal dose (SED) that is increasingly used as the exposure unit in epidemiologic and laboratory studies. The SED is independent of personal UVR sensitivity and emission spectrum and is set as an exposure of 100 J/m^2.

Another measure of UVR exposure that is more easily understood is the UV index, which is used worldwide to promote public awareness of the risks of UVR exposure and sun protection.[11] The UV index, which is also based on the erythema action spectrum, is directly proportional to the intensity of erythemal UVR. The values vary with sun elevation, so by time of day, time of year, and latitude, and also with altitude, ozone, cloud cover, and ground reflection.

CAPSULE SUMMARY

- Acute effects of ultraviolet radiation exposure include erythema, pigmentation, suppression of acquired immunity, enhancement of innate immunity, and vitamin-D synthesis. Chronic effects include photocarcinogenesis and photoaging.
- Photoprotection, including the application of sunscreens, has been shown to inhibit many of the acute and chronic effects of ultraviolet radiation exposure.

DNA damage

The effects of UVR in the skin are initiated at a molecular level involving epidermal and dermal chromophores that absorb UV or visible radiation, each with a characteristic absorption spectrum. When such a chromophore absorbs photon energy, it moves to a higher energy ("excited") state and becomes unstable. This may result in either a structural change, binding to other molecules that define a "direct effect," or acting as a sensitizer generating reactive oxygen species that damage adjacent biomolecules such as DNA or proteins (indirect effects). In the excited state, chromophores are the initiators of all short- and long-term photobiological responses.[2,12] Endogenous skin chromophores include DNA, melanins, and their precursors, urocanic acid, aromatic amino acids, flavins, and porphyrins. Exogenous chromophores include photosensitizing drugs, eg, fluoroquinolones and azathioprine (inadvertent photosensitization), 8-methoxypsoralen as used in psoralen plus UVA therapy for psoriasis (deliberate photosensitization), and sunscreens. DNA, which absorbs solar UVB and some UVA, is probably the most important endogenous chromophore. The most frequent photolesions are cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6-4) pyrimidones. These result in structural damage to the DNA helix inhibiting DNA replication and transcription. CPDs are the most common and the most damaging type of lesion. Relatively low and even suberythemal doses of UVB have been shown to cause a high amount of DNA damage in the epidermis.[13]

CPDs provoke cytokine-mediated inflammation leading to erythema and concomitant immunosuppression and transition mutations, such as C (cytosine) → T (thymine) or even CC → TT, which can lead to keratinocyte cancers (KCs). Less is known about the relationship of melanoma with CPDs, although intense, intermittent UVR exposure is significantly associated with melanoma risk.[14]

Table I. Main effects of ultraviolet radiation on normal-appearing human skin

Acute		
Molecular/cellular	**Clinical**	**Chronic**
• DNA photodamage (and its repair) → mutation (C → T, CC → TT)	• Erythema	• Skin cancer
• Reactive oxygen species	• Tanning	• Photoaging
• Gene and protein expression	• Suppression of acquired immunity	
• Melanogenesis	• Enhancement of innate immunity	
• Apoptosis	• Reduction of blood pressure via nitric oxide	
• Langerhans cell depletion		
• Vitamin-D photosynthesis		
• Nitric oxide release (UVA)		

C, Cytosine; *T*, thymine; *UV*, ultraviolet.

Table II. Fitzpatrick skin type and ultraviolet radiation response

Skin type	Skin color (protected)	Susceptibility to sunburn	1 MED (as SED)	Tanning ability	Susceptibility to skin cancer
I	White	Very readily	2-3	Never tans	Very high
II	White	Readily	3-4	Tans minimally	Very high
III	White	Moderately	4-5	Average tanning	High
IV	Olive	Occasionally	5-6	Tans easily	Moderate
V	Brown	Rarely	8-12	Tans easily and substantially	Low
VI	Black/dark brown	Never/rarely	16-24	Tans readily and profusely	Low

MED, Minimal erythemal dose; *SED*, standard erythemal dose.

Melanoma is a very heterogeneous disease and investigations are ongoing into other mechanisms by which it may be induced. It is estimated that UVR exposure is associated with 65% of melanoma cases and 90% of KC.[15] CPD also triggers the expression of matrix metalloproteinase (MMP)-1, which degrades collagen and is responsible for photoaging.[16] Epidermal CPDs and pyrimidine (6-4) pyrimidones are removed mainly through nucleotide excision repair, a process that plays a vital role in protecting against DNA damage. This can be seen clearly in patients with xeroderma pigmentosum, whose capacity for DNA damage repair is impaired. These individuals have a more than 10,000-fold greater risk for KC and greater than 2000-fold increased risk of melanoma before age 20 years.[17] Repair of CPDs is slow (>24 hours), so damage may accumulate with repeated UVR daily exposure.

PHOTOPROTECTION BY SUNSCREENS

Sunscreens were originally developed to minimize erythema (sunburn), the action spectrum of which shows that UVB is about 1000 times more effective than UVA per unit dose (J/m^2). Thus, early sunscreens were primarily UVB absorbers. Erythema is the end point of the main index of sunscreen efficacy, namely the SPF, which is mainly, but not exclusively, an index of UVB protection. However, both animal and human studies have shown that other acute and chronic pathogenic effects may occur after cumulative exposure to suberythemal doses of solar UVR, including UVA. It was therefore recognized that for protection against damage other than sunburn, an ideal sunscreen should protect against the entire solar UVB/UVA range.

At the same time, it is necessary to avoid blocking the beneficial effects of UVR such as vitamin-D synthesis, photoadaptation (natural protection for the skin), immunosuppression of acquired immunity, induction of innate immunity, and more recently identified benefits such as reduction in blood pressure by UVA.[4]

Sunscreen regulation

Regulatory standards for sunscreens differ around the world. In the United States sunscreens are regarded as over-the-counter drugs (Table III),[18] and in Canada they are considered drugs unless they contain only titanium dioxide, zinc oxide, or para-aminobenzoic acid, where they are defined as "natural health products."[19] (This policy is currently under review by Health Canada.) Most sunscreens in Australia, including primary sunscreens with SPF 4 or higher, are regarded as "therapeutic goods" and must be registered with the Australian Register of Therapeutic Goods.[20] Elsewhere, including the

Table III. Ultraviolet filters listed in the US Food and Drug Administration final monograph[18]

Active ingredient, USAN	Peak absorption (λ_{max}) or absorption range (nm)
UVB filters	
Aminobenzoic acid	283
Padimate O	311
Octinoxate	311
Cinoxate	289
Octisalate	307
Homosalate	306
Trolamine salicylate	260-355
Octocrylene	303
Ensulizole	310
UVA filters	
Oxybenzone	288,325
Sulisobenzone	366
Dioxybenzone	352
Avobenzone	360
Meradimate	340
Inorganic filters	
Titanium dioxide	UVB-UVA*
Zinc oxide	UVB-UVA*

USAN, US adopted name; *UV*, ultraviolet.
*Absorption varied depending on the particle size.

European Union, China, India, Japan, and members of Association of Southeast Asian Nations and Mercado Común del Sur in South America, sunscreens are defined as cosmetics, although by differing criteria.[21] As a result of these differences in regulatory processes for sunscreens, fewer products are available in the United States and Canada than in most of the rest of the world. For example, no new UVR filters have been approved in North America since 2002.[22,23] In the United States in 2015, the Food and Drug Administration (FDA) rejected applications for the use of 8 new UVR filters in sunscreens, despite those filters already being in use in Europe, without additional information, including percutaneous absorption safety data.[22] At the time of writing, no progress has been made on the approval process.

Despite initiatives toward harmonization of sunscreen testing and labeling, many variations remain worldwide. SPF, first introduced by Schulze[24] in 1956, is calculated as the ratio of the doses of solar-simulated radiation causing erythema with sunscreen applied to that without sunscreen. Published by the International Standards Organization (ISO) in 2010,[25] the ISO 24444 international standard specifying a method for the in vivo determination of the SPF of sunscreen products has been adopted as the SPF evaluation standard worldwide, including in Europe, Canada, Australia, and Japan. In the United States, the same year, the FDA issued its final rule on labeling and effectiveness testing of "sunscreen drug products."[18,26] The FDA SPF is similar to that of ISO 24444 and SPF values obtained by 2 methods are comparable. Both apply a standardized sunscreen dose of 2 mg/cm^2 for in vivo testing. Both the ISO and FDA standards are accepted by many countries worldwide in addition to their own standards (Table IV). An SPF value of 50+ is the maximum allowable SPF on sunscreen product labels in many countries, including Europe, Australia, and Japan, although in practice the SPF may be higher. Of note, the US FDA has not yet made its final ruling on the maximal allowable SPF on labels. Despite efforts to harmonize methods for evaluation of SPF, however, regulations for SPF claims for sunscreen products vary widely between different countries. No standardized in vitro method of SPF testing has been recommended to date.

Both the ISO and the FDA have addressed UVA testing. In 2011 the ISO issued ISO 24442,[27] a standard for an in vivo method to determine the UVA protection factor of a sunscreen product using a persistent pigment-darkening method based on the recommendation of the Japan Cosmetic Industry Association.[28,29] However, Japan is now the only region to require a mandatory in vivo test for UVA protection. ISO 24443, issued in 2012, sets out an in vitro procedure to create a UVR spectral absorbance curve as the basis for determining UVA protection parameters such as the UVA protection factor, critical wavelength, and UVA absorbance proportionality.[30] Of these parameters, the FDA chose the in vitro critical wavelength test, defined as the wavelength below which 90% of the total area under the absorbance (290-400 nm) curve resides.[18] A critical wavelength of 370 nm or greater is required for sunscreens to be labeled as "broad spectrum." The European Union recommends both a critical wavelength of more than 370 nm and UVA protection factor at least one third of the labeled SPF as the criterion for labeling as either UVA or broad-spectrum protection.[30]

Other testing required for sunscreens involves in vivo determination of water resistance. "Waterproof" claims are no longer accepted because they imply complete protection while bathing or perspiring. Methods for testing for water resistance in Europe and the United States are based on comparison of the SPF of a sunscreen before and after it has been immersed in water for a specific period. To be designated as "water resistant" in Europe, the SPF measured must be 50% or more of its level measured before two 20-minute periods of water immersion, according to guideline issued by Cosmetics Europe—the Personal Care Association

Table IV. Worldwide implementation of Food and Drug Administration final monograph (2011)[18] and International Standards Organization standards[24,26,29] for sunscreen evaluation

Region	SPF in vivo	UVA PF in vivo	UVA PF in vitro
Europe	ISO 24444:2010	ISO 24442:2011	ISO 24443:2012
United States	FDA 2011	Not required	FDA 2011
Canada	ISO 24444:2010 FDA 2011	ISO 24442:2011	FDA 2011 ISO 24443:2012
Mexico	ISO 24444:2010 FDA 2011	ISO 24442:2011	FDA 2011 ISO 24443:2012
MERCOSUR*	ISO 24444:2010 FDA 2011	ISO 24442:2011	ISO 24443:2012
South Africa	ISO 24444:2010	ISO 24442:2011	ISO 24443:2012
India	ISO 24444:2010 FDA 2011	ISO 24442:2011	FDA 2011 ISO 24443:2012
Japan	ISO 24444:2010	ISO 24442:2011	Not required
Korea	ISO 24444:2010	ISO 24442:2011	Not required
ASEAN†	ISO 24444:2010	ISO 24442:2011	ISO 24443:2012
Australia	ISO 24444:2010	Not required	ISO 24443:2012

ASEAN, Association of Southeast Asian Nations; *FDA*, Food and Drug Administration; *ISO*, International Standards Organization; *MERCOSUR*, Mercado Común del Sur; *PF*, protection factor; *SPF*, sun-protection factor; *UV*, ultraviolet.
*Argentina, Brazil, Paraguay, Uruguay, and Venezuela.
†Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam.

(formerly the European Cosmetic, Toiletry, and Perfumery Association).[31] For a brand to claim to be "very water resistant," the test is conducted for 4 periods of 20 minutes. In contrast, to make the above claims, the FDA requires that the SPF value after water immersion is the same as the value before immersion.[18]

Although it is important to confirm the photostability of a sunscreen over the whole UVA and UVB ranges, photostability testing is not mandatory in Europe, Australia, or the United States; however, the FDA requires the sample to be preirradiated to establish its photostability for the critical wavelength test.[25,26] Photostability of a product may also be determined by an in vivo method in which a fixed amount of sunscreen is applied on the skin of a test subject followed by irradiation. The UVR filters are recovered by tape stripping and extracted from the tapes, and their residual presence is quantified by high-performance liquid chromatography and spectrophotometry. The difference between the amounts of product before and after irradiation is the basis of this test. In 2004, Cosmetics Europe issued a comparable in vitro testing guideline, which was also based on the high-performance liquid chromatography determination of the UVR filter amount of a tested sun-protection product before and after UV irradiation.[32]

Real-life sunscreen use

Numerous studies have recorded that, in real life, people typically apply much less sunscreen than the dose (2 mg/cm^2) used in the SPF testing process.[33-40] This varies between 0.5 and 1.5 mg/cm^2. Most real-life users probably achieve a mean value of between 20% and 50% of the labelled SPF.[41-43] It has been said, provocatively, that if sunscreens were applied appropriately to prevent sunburn there would be no need for SPFs greater than 15.[44] There have been calls for modification of testing methods[42] and for products to be labeled more clearly and realistically.[43] The relation between sunscreen application thickness and SPF is unclear. Some investigators have reported that it is linear[42,45] and others that it is exponential.[46-48] The reason for the different findings is unknown, but it may be a result of variations in formulation (vehicles and properties of sun filters), and the concentration of active ingredients.

SUNSCREENS IN SKIN CANCER PREVENTION

In animal studies, a sunscreen (SPF 12) was shown to protect against epidermal cell damage using UVB-induced "sunburn cells" (apoptotic keratinocytes) as an end point.[49] UVR-induced immunosuppression is important in skin cancer development. A sunscreen (SPF 15) containing 2-ethylhexyl-p-methoxycinnamate was found to protect against systemic suppression of contact hypersensitivity to 2,4-dinitrofluorobenzene, and induction of susceptibility to transplanted UVR-induced tumor cells.[50,51] Application of SPF-15 sunscreens to mouse skin nearly abolished

UVR-induced mutations in the *p53* tumor suppressor gene.[52]

Immunosuppression

In a United Kingdom study in 119 white volunteers, solar-simulated radiation exposure of previously unexposed buttock skin with and without sunscreen (SPF 15) induced a UVR dose-dependent suppression of the contact hypersensitivity response, but for a given UVR dose, contact hypersensitivity responses were higher with than without sunscreen.[53] The sunscreen also protected against erythema, but protection against immunosuppression was less than half that for erythema, which the investigators concluded was probably a result of immunosuppression by UVA, because the sunscreen was primarily a UVB absorber. Evaluation of 2 broad-spectrum SPF 15 sunscreens showed an unaltered local delayed-type hypersensitivity response to recall antigens after a single solar-simulated radiation exposure in the group pretreated with the sunscreen product with higher protection in the UVA range but was significantly suppressed by 55.7% in the group pretreated with sunscreen with a much lower UVA protection, indicating that UVA is highly involved in immunosuppression.[54]

DNA photodamage

The efficacy of daily application of a broad-spectrum SPF 15 sunscreen in protecting against UVR-induced epidermal DNA damage (CPD) was demonstrated by its application on buttock sites of 18 women 30 minutes before exposure to 2 MED of solar-simulated radiation over 4 days.[55] One site was treated daily, 3 sites were treated on 3 irradiation days, and 1 site was not irradiated (control). There was no significant difference in CPD between nonirradiated and irradiated skin when sunscreen application preceded each irradiation, but when sunscreen application was omitted even once before irradiation, there was a statistically significant increase in CPD. This study showed that regular use of a broad-spectrum sunscreen is effective in preventing UVR-induced DNA damage, but that irregular and inadequate use of sunscreen during exposure to UVR results in CPD formation, which may lead to mutation and subsequent cancer development. The ability of a broad-spectrum, SPF 30 sunscreen to protect against UVR-induced tissue alterations and DNA damage was investigated using engineered human skin exposed to increasing doses of solar-simulated radiation.[56] Sunscreen significantly reduced the frequencies of CPDs, pyrimidine (6-4) pyrimidones, and photo-oxidative damage to DNA. A recent study (Young et al, unpublished data, 2016) evaluated DNA protection by sunscreen in 16 subjects with sun-sensitive skin after application of a broad-spectrum sunscreen SPF 50+ at 0.75, 1.3, and 2.0 mg/cm^2. Topically treated sites were exposed to 30 SED (corresponding to 3 hours of sun exposure during summer in Brazil or Australia), and compared with 4 SED with no sunscreen, in an acute exposure group. Holiday sun behavior simulated by 5 consecutive days of exposure to 15 and 30 SED with sunscreen was compared with 1 SED with no sunscreen. In all cases the sunscreen-treated sites had fewer CPD than nonprotected sites and DNA protection was dependent on sunscreen application thickness.

Actinic keratoses

Actinic keratoses (AKs) are markers of chronic photodamage of the skin. The major associated factors are male sex, advanced age, sun-sensitive complexion, high lifetime sun exposure, and prolonged immunosuppression. Primary prevention of AKs is achieved by limiting intense sun exposure. Several randomized controlled trials have demonstrated that regular use of sunscreens prevents AKs, potentially reducing the risk of skin cancer over the long term. The effect of broad-spectrum sunscreen (SPF 17) was tested in a landmark Australian summer study in 588 adults aged 40 years or older with AKs.[57] The patients applied either a sunscreen or base cream only to the head, neck, forearms, and hands. The mean number of AKs increased by 1.0 per patient in the base-cream group and decreased by 0.6 in the sunscreen group, with fewer new lesions and more remissions in the latter. There was a sunscreen dose-response effect: the amount of sunscreen used was related to both the development of new lesions and the remission of existing ones. A US study, undertaken in a high-risk population in Texas, investigated daily application of sunscreen (SPF 29) vs placebo over a 2-year period.[58] The 53 participants had previously demonstrated AK or KC, continuing sun exposure, and were not regular sunscreen users. At the end of study, the rate of appearance of new precancerous skin lesions was less for the treatment group than for the control group. The Nambour Skin Cancer Prevention Trial, carried out in an Australian community in a subtropical environment (Queensland, Australia) showed that AKs can be prevented by regular sunscreen application to the head, neck, hands, and forearms.[59] A total of 1621 adults aged 25 to 74 years were randomized to daily use of a provided sunscreen (application of an SPF 16 sunscreen every morning) or application of their own sunscreen at their usual discretionary rate. The ratio of AK counts over 2-year

period was 24% lower, and the rate of AK acquisition was 44% lower in people randomized to daily sunscreen use than in those randomized to discretionary sunscreen use, equivalent to the prevention of an average of 1 additional AK per person during that time.

Keratinocyte cancer

KC is the most common cancer worldwide and the most frequently observed malignancy in people with white skin. Approximately 75% to 80% of KCs are basal cell carcinomas (BCCs) and 20% to 25% are squamous cell carcinomas (SCCs), the majority of cases occur on the head and neck, and solar UVR is the predominant causative agent. The Nambour Skin Cancer Prevention Trial showed that regular sunscreen use can inhibit SCC but not BCC. Among 1383 participants who underwent a full skin examination by a dermatologist, 250 developed 758 new skin cancers during the follow-up period of 4.5 years.[60] There were no significant differences in the incidence of first new skin cancers (BCC or SCC) between groups randomly assigned daily sunscreen and discretionary sunscreen use. However, the number of SCC tumors was significantly lower (39%) in the sunscreen group than in the discretionary sunscreen group ($P < .05$), with an even greater (52%) reduction when only histologically confirmed tumors were analyzed. As part of the 2×2 factorial design of the study some patients were also randomized to β-carotene supplementation (30 mg/d) vs placebo tablets, but no beneficial or harmful effects of β-carotene were noted. After completion of the trial, participants were followed up for a further 8 years and during this time, BCC tumor rates tended to decrease but not significantly in people formerly randomized to daily sunscreen use compared with the discretionary use group.[61] In contrast, corresponding SCC tumor rates decreased significantly by almost 40% during the entire follow-up period, confirming the prolonged preventive effects of sunscreen use on SCC but no clear benefit in reducing BCC.

In a single-center study of 120 organ transplant recipients, 60 recipients of a liver, kidney, or heart transplant used a broad-spectrum sunscreen (SPF ≥50, high UVA protection) for daily application to the head, neck, forearms, and hands for 24 months.[62] At the same time 60 control subjects matched for age, type of transplant, and time since transplantation were given only standard advice about sun protection and told to use commercially available sunscreens of their own choice. Patients in the sun-protection intervention group had a partial remission of AKs (−120 lesions vs +82 in the control group, $P < .01$) and less frequent development of SCC (0 vs 8, $P < .01$) and BCC (2 vs 9, not statistically significant). Daily application of sunscreen is now a standard recommendation for immunosuppressed patients.

Melanoma

High melanocytic nevus density has been established as a strong predictor of melanoma in a number of studies using different methods of evaluation.[63-69] In adults younger than 30 years, 50% of cutaneous melanomas are associated with a melanocytic nevus precursor.[70] The regular use of sunscreen (broad-spectrum, SPF 30) was first shown to reduce the number of nevi in children in a randomized, controlled study in 2000.[71] The study included 309 white schoolchildren age 6 to 10 years who either regularly used SPF 30 sunscreen (sunscreen group) or received no sunscreen or advice about sunscreen (control group). After 3 years, the median number of nevi was 24 in the sunscreen group vs 28 in the control group ($P = .048$). Modeling of the data suggested that regular use of sunscreen in this group would prevent 30% to 40% of nevi compared with no sunscreen use. Further analysis showed that children randomized to the sunscreen group had significantly fewer new nevi on the trunk, and fewer nevi on the lower limbs compared with children in the control group, supporting the hypothesis of site-specific differences in nevus potential and the sunscreen's protective effect.[72]

The Nambour trial was the first randomized study to show that the daily application of a broad-spectrum sunscreen (SPF 16) can reduce the risk of melanoma in 1621 participants aged 25 to 75 years.[73] Ten years after the treatment phase of the trial ended, 11 new primary melanomas had been identified in the daily sunscreen group, and 22 had been identified in the discretionary group, a reduction of 50% in the daily sunscreen group compared with discretionary use (hazard ratio 0.50, 95% confidence interval, 0.24-1.02; $P = .051$). The effect was even greater for invasive melanomas by 73% (hazard ratio 0.27, 95% confidence interval 0.08-0.97; $P = .045$). The decrease in melanoma was seen across all body sites, not only prescribed application sites. Given the results of the earlier study in children, the Nambour investigators suggest that a long-term sunscreen intervention among children and adolescents may yield even greater benefits in cancer prevention than seen in adults.

Photoaging

Photoaging, clinically and histologically distinct intrinsic skin aging, is associated with increased

elastosis and collagen fragmentation below the dermoepidermal junction. There are few data on the role of sunscreens in preventing photoaging for which both UVA and UVB have been implicated. One human study has shown that the erythema action spectrum predicts the induction of MMP-1 messenger RNA, which suggested that UVB is much more important.[74] In a study of 35 adults given a diagnosis of AKs, skin cancer, or both, solar elastosis was significantly diminished by at least twice-daily application of a sunscreen consisting of 7% octylethoxycinnamate, 6% oxybenzone, and 5% octyl salicylate, blocking UVB and short-wavelength UVA compared with a vehicle placebo over 2 years.[75] A highly photostable sunscreen (high UVA protection factor 22) was shown to provide high protection against multiple cellular markers of photoaging (MMP-1 and MMP-9) and sunburn cells, Langerhans cell depletion, CPD, and p53 expression.[76] These markers were evaluated in biopsy specimens from 12 subjects after 4 treatments: unprotected exposed to 0, 1, or 3 MED solar-simulated radiation and sunscreen (SPF 55) protected exposed to 55 MED. All the markers showed significantly more damage with 3 MED-untreated sites compared with nonirradiated control, and most showed marked damage after unprotected 1 MED exposure. After 55 MEDs, sunscreen-protected sites showed significantly less p53 and MMP-9 in keratinocytes than the 1 MED-exposed unprotected sites, suggesting that the sunscreen provided better protection against cellular damage than its SPF indicated. The other biomarkers in sunscreen protected sites showed no statistical differences from 1 MED-exposed unprotected sites, indicating that significant protection was present at cellular and molecular levels even with a very high solar-simulated radiation exposure. The Nambour trial (see above) was the first to show the effect of daily sunscreen use over 4.5 years on skin aging in human beings with respect to clinical signs of photoaging and in a large patient group.[77] Skin aging from baseline to the end of the trial was 24% less in the daily sunscreen group than in the discretionary sunscreen group (relative odds 0.76, 95% confidence interval 0.59-0.98).

Summary

There is ample evidence to demonstrate the acute and chronic skin alterations caused by solar range UVR, and the benefits that sunscreens afford in the reduction and even prevention of such changes.

The efficacy of sunscreens can be assessed by different methods, more or less robust, involving in vitro, ex vivo, or in vivo measurements. There is a need for a worldwide standardization of these methods to avoid misunderstanding and confusion among sunscreen users. Despite the development of new filters systems and broad-spectrum products, education of consumers and patients regarding the application of sunscreens, both in terms of quantity and quality, should be a priority for dermatologists and public health organizations. Many questions remain regarding the exact level of protection for each hazardous sun effect on our skin. New robust methods for evaluation of sunscreens efficacy have been developed in recent years, including quantitative analysis of UVR damage (transcriptomic and proteomic analyses, 2-photon fluorescence microscopy, immunohistochemistry) and may help to differentiate the efficacies of different sunscreens formulations in the future.

REFERENCES

1. Baron ED, Suggs AK. Introduction to photobiology. *Dermatol Clin*. 2014;32:255-266.
2. Young AR. Acute effects of UVR on human eyes and skin. *Prog Biophys Mol Biol*. 2006;92:80-85.
3. Liu D, Fernandez BO, Hamilton A, et al. UVA irradiation of human skin vasodilates arterial vasculature and lowers blood pressure independently of nitric oxide synthase. *J Invest Dermatol*. 2014;134:1839-1846.
4. Johnson RS, Titze J, Weller R. Cutaneous control of blood pressure. *Curr Opin Nephrol Hypertens*. 2016;25:11-15.
5. Matsumura Y, Ananthaswamy HN. Short-term and long-term cellular and molecular events following UV irradiation of skin: implications for molecular medicine. *Expert Rev Mol Med*. 2002;4:1-22.
6. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. *Arch Dermatol*. 1988;124:869-871.
7. Harrison GI, Young AR. Ultraviolet radiation-induced erythema in human skin. *Methods*. 2002;28:14-19.
8. McKinlay AF, Diffey BL. A reference action spectrum for ultraviolet induced erythema in human skin. *CIE J*. 1987;6:17-22.
9. Commission Internationale de l'Eclairage. *Erythema reference action spectrum and standard erythema dose*. ISO 17166:1999 (CIE S 007/E-1998). Vienna, Austria: Commission Internationale de l'Eclairage; 1998.
10. Webb AR, Slaper H, Koepke P, Schmalwieser AW. Know your standard: clarifying the CIE erythema action spectrum. *Photochem Photobiol*. 2011;87:483-486.
11. Acosta LR, Archer CB, Armstrong B, et al. *Global UV index: a practical guide. A joint recommendation of the World Health Organization, World Meteorological Organization, United Nations Environment Program, and the International Commission on Non-Ionizing Radiation Protection*. WHO/SDE/OEH/02.2. Geneva, Switzerland: World Health Organization; 2002.
12. Young AR. Chromophores in human skin. *Phys Med Biol*. 1997;42:789-802.
13. Seité S, Fourtanier A, Moyal D, Young AR. Photodamage to human skin by suberythemal exposure to solar ultraviolet radiation can be attenuated by sunscreens: a review. *Br J Dermatol*. 2010;163:903-914.
14. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer*. 2005;41:45-60.

15. Pleasance ED, Cheetham RK, Stephens PJ, et al. A comprehensive catalogue of somatic mutations from a human cancer genome. *Nature*. 2010;463:191-196.
16. Poon F, Kang S, Chien AL. Mechanisms and treatments of photoaging. *Photodermatol Photoimmunol Photomed*. 2015; 31:65-74.
17. Bradford PT, Goldstein AM, Tamura D, et al. Cancer and neurologic degeneration in xeroderma pigmentosum: long term follow-up characterizes the role of DNA repair. *J Med Genet*. 2011;48:168-176.
18. Department of Health and Human Services, US Food and Drug Administration (FDA). 21 CFR 201.327. FDA-1978-N-0018-0698. Labeling and effectiveness testing; sunscreen drug products for over-the-counter human use. Final rule. *Fed Regist*. 2011;76:35620-35665.
19. Health Canada. *Health Products and Food Branch. Sunscreen monograph*. Version 2.0. Ottawa, Canada: Health Canada; 2013. Available from: URL: http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=sunscreen-ecransolaire&. Accessed May 3, 2016.
20. Australian Government, Department of Health, Therapeutic Goods Administration. *Australian regulatory guidelines for sunscreens. Version 1.1, January 2016*. Woden, ACT, Australia: Therapeutic Goods Administration; 2016. Available from: URL: https://www.tga.gov.au/publication/australian-regulatory-guidelines-sunscreens-args. Accessed April 22, 2016.
21. Stiefel C, Schwack W. Photoprotection in changing times — UV filter efficacy and safety, sensitization processes and regulatory aspects. *Int J Cosmet Sci*. 2015;37:2-30.
22. Reisch MS. After more than a decade, FDA still won't allow new sunscreens. *Chem Eng News*. 2015;93:10-15.
23. Sharfstein JM. A spotlight on sunscreen regulation. *N Engl J Med*. 2015;373:101-103.
24. Schulze R. Einige Versuche und Bemerkungen zum Problem der handelsüblichen Lichtschutzmittel. *Parf Kosm*. 1956;37: 310-315.
25. Technical Committee ISO/TC 217, Cosmetics. ISO 24444: 2010. *Cosmetics — sun protection test methods — in vivo determination of the sun protection factor (SPF)*. Geneva, Switzerland: International Organization for Standardization; 2010.
26. Wang SQ, Lim HW. Current status of the sunscreen regulation in the United States: 2011 Food and Drug Administration's final rule on labeling and effectiveness testing. *J Am Acad Dermatol*. 2011;65:863-869.
27. International Organization for Standardization. ISO 24442: 2011. *Cosmetics — sun protection test methods — in vivo determination of sunscreen UVA protection*. Geneva, Switzerland: International Organization for Standardization; 2011.
28. Japan Cosmetic Industry Association. *Measurement standards for UVA protection efficacy*. Issued November 21, 1995 and effective as of January 1, 1996. Tokyo, Japan: Japan Cosmetic Industry Association (JCIA); 1995.
29. Moyal D, Wichrowski K, Tricaud C. In vivo persistent pigment darkening method: a demonstration of the reproducibility of the UVA protection factors results at several testing laboratories. *Photodermatol Photoimmunol Photomed*. 2006;22: 124-128.
30. International Organization for Standardization. ISO 24443: 2012. *Determination of sunscreen UVA photoprotection in vitro*. Geneva, Switzerland: International Organization for Standardization; 2012.
31. Cosmetics Europe. *Cosmetics Europe: Guidelines for evaluating sun product water resistance*. Brussels, Belgium: Cosmetics Europe; 2005. Available from: URL: https://cosmeticseurope.eu/publications-cosmetics-europe-association/guidelines.html?view=item&id=18. Accessed January 15, 2016.
32. Cosmetics Europe. *Cosmetics Europe: Guidelines on stability testing of cosmetic products*. Brussels, Belgium: Cosmetics Europe; 2004. Available from: URL: https://www.cosmeticseurope.eu/publications-cosmetics-europe-association/guidelines.html?view=item&id=20%3Aguidelines-on-stability-testing-of-cosmetics-cectfa-2004&catid=46%3Aguidelines. Accessed January 15, 2016.
33. Stenberg C, Larkö O. Sunscreen application and its importance for the sun protection factor. *Arch Dermatol*. 1985;121: 1400-1402.
34. Bech-Thomsen N, Wulf HC. Sunbathers' application of sunscreen is probably inadequate to obtain the sun protection factor assigned to the preparation. *Photodermatol Photoimmunol Photomed*. 1992—1993;9:242-244.
35. Azurdia RM, Pagliaro JA, Diffey BL, Rhodes LE. Sunscreen application by photosensitive patients is inadequate for protection. *Br J Dermatol*. 1999;140:255-258.
36. Autier P, Boniol M, Severi G, Doré JF. European Organization for Research and Treatment of Cancer Melanoma Co-operative Group. Quantity of sunscreen used by European students. *Br J Dermatol*. 2001;144:288-291.
37. Reich A, Harupa M, Bury M, et al. Application of sunscreen preparations: a need to change the regulations. *Photodermatol Photoimmunol Photomed*. 2009;25:242-244.
38. Yang HP, Chen K, Ju M, et al. A study of the way in which dermatologists and photosensitive patients apply sunscreen in China. *Photodermatol Photoimmunol Photomed*. 2009;25: 245-249.
39. Bauer U, O'Brien DS, Kimlin MG. A new method to quantify the application thickness of sunscreen on skin. *Photochem Photobiol*. 2010;86:1397-1403.
40. De Villa D, Nagatomi AR, Paese K, et al. Reapplication improves the amount of sunscreen, not its regularity, under real life conditions. *Photochem Photobiol*. 2011;87:457-460.
41. Petersen B, Wulf HC. Application of sunscreen—theory and reality. *Photodermatol Photoimmunol Photomed*. 2014;30:96-101.
42. Diffey B. Sunscreen isn't enough. *J Photochem Photobiol B*. 2001;64:105-108.
43. Wulf HC, Stender IM, Lock-Andersen J. Sunscreens used at the beach do not protect against erythema: a new definition of SPF is proposed. *Photodermatol Photoimmunol Photomed*. 1997;13:129-132.
44. Diffey B. Has the sun protection factor had its day? *Br J Dermatol*. 2000;320:176-177.
45. Bimczok R, Gers-Barlag H, Mundt C, et al. Influence of applied quantity of sunscreen products on the sun protection factor — a multicenter study organized by the DGK Task Force Sun Protection. *Skin Pharmacol Physiol*. 2007;20:57-64.
46. Faurschou A, Wulf HC. The relation between sun protection factor and amount of sunscreen applied in vivo. *Br J Dermatol*. 2007;156:716-719.
47. Kim SM, Oh BH, Lee YW. The relation between the amount of sunscreen applied and the sun protection factor in Asian skin. *J Am Acad Dermatol*. 2010;62:218-222.
48. Schalka S, Dos Reis VM, Cucé LC. The influence of the amount of sunscreen applied and its sun protection factor (SPF): evaluation of two sunscreens including the same ingredients at different concentrations. *Photodermatol Photoimmunol Photomed*. 2009;25:175-180.
49. Sambuco CP, Forbes PD, Davies RE, Urbach F. An animal model to determine sunscreen protectiveness against both vascular injury and epidermal cell damage. *J Am Acad Dermatol*. 1984;10(5 Pt 1):737-743.

50. Reeve VE, Bosnic M, Boehm-Wilcox C, Ley RD. Differential protection by two sunscreens from UV radiation-induced immunosuppression. *J Invest Dermatol*. 1991;97:624-628.
51. Roberts LK, Beasley DG. Commercial sunscreen lotions prevent ultraviolet-radiation-induced immune suppression of contact hypersensitivity. *J Invest Dermatol*. 1995;105: 339-344.
52. Ananthaswamy HN, Loughlin SM, Cox P, et al. Sunlight and skin cancer: inhibition of p53 mutations in UV-irradiated mouse skin by sunscreens. *Nat Med*. 1997;3:510-514.
53. Kelly DA, Seed PT, Young AR, Walker SL. A commercial sunscreen's protection against ultraviolet radiation-induced immunosuppression is more than 50% lower than protection against sunburn in humans. *J Invest Dermatol*. 2003;120: 65-71.
54. Moyal DD, Fourtanier AM. Efficacy of broad-spectrum sunscreens against the suppression of elicitation of delayed-type hypersensitivity responses in humans depends on the level of ultraviolet A protection. *Exp Dermatol*. 2003;12:153-159.
55. Al Mahroos M, Yaar M, Phillips TJ, et al. Effect of sunscreen application on UV-induced thymine dimers. *Arch Dermatol*. 2002;138:1480-1485.
56. Bissonauth V, Drouin R, Mitchell DL, et al. The efficacy of a broad-spectrum sunscreen to protect engineered human skin from tissue and DNA damage induced by solar ultraviolet exposure. *Clin Cancer Res*. 2000;6:4128-4135.
57. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. *N Engl J Med*. 1993;329:1147-1151.
58. Naylor MF, Boyd A, Smith DW, et al. High sun protection factor sunscreens in the suppression of actinic neoplasia. *Arch Dermatol*. 1995;131:170-175.
59. Darlington S, Williams G, Neale R, et al. A randomized controlled trial to assess sunscreen application and beta carotene supplementation in the prevention of solar keratoses. *Arch Dermatol*. 2003;139:451-455.
60. Green A, Williams G, Neale R, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomized controlled trial. *Lancet*. 1999;354:723-739.
61. van der Pols JC, Williams GM, Pandeya N, et al. Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. *Cancer Epidemiol Biomarkers Prev*. 2006;15: 2546-2548.
62. Ulrich C, Jürgensen JS, Degen A, et al. Prevention of non-melanoma skin cancer in organ transplant patients by regular use of a sunscreen: a 24 months, prospective, case-control study. *Br J Dermatol*. 2009;161(Suppl 3):78-84.
63. Holly EA, Kelly JW, Shpall SN, Chiu SH. Number of melanocytic nevi as a major risk factor for malignant melanoma. *J Am Acad Dermatol*. 1987;17:459-468.
64. Garbe C, Kruger S, Stadler R, et al. Markers and relative risk in a German population for developing malignant melanoma. *Int J Dermatol*. 1989;28:517-523.
65. MacKie RM, Freudenberger T, Aitchison TC. Personal risk-factor chart for cutaneous melanoma. *Lancet*. 1989;2: 487-490.
66. Augustsson A, Stierner U, Rosdahl I, Suurkula M. Common and dysplastic nevi as risk factors for cutaneous malignant melanoma in a Swedish population. *Acta Derm Venereol*. 1991;71:518-524.
67. Garbe C, Buttner P, Weiss J, et al. Risk factors for developing cutaneous melanoma and criteria for identifying persons at risk: multicenter case-control study of the Central Malignant Melanoma Registry of the German Dermatological Society. *J Invest Dermatol*. 1994;102:695-699.
68. Bataille V, Bishop JA, Sasieni P, et al. Risk of cutaneous melanoma in relation to the numbers, types and sites of nevi: a case-control study. *Br J Cancer*. 1996;73:1605-1611.
69. Tucker MA, Halpern A, Holly EA, et al. Clinically recognized dysplastic nevi: a central risk factor for cutaneous melanoma. *JAMA*. 1997;277:1439-1444.
70. Tsao H, Bevona C, Goggins W, Quinn T. The transformation rate of moles (melanocytic nevi) into cutaneous melanoma: a population-based estimate. *Arch Dermatol*. 2003;139: 282-288.
71. Gallagher RP, Rivers JK, Lee TK, et al. Broad-spectrum sunscreen use and the development of new nevi in white children: a randomized controlled trial. *JAMA*. 2000;283:2955-2960.
72. Lee TK, Rivers JK, Gallagher RP. Site-specific protective effect of broad-spectrum sunscreen on nevus development among white schoolchildren in a randomized trial. *J Am Acad Dermatol*. 2005;52:786-792.
73. Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. *J Clin Oncol*. 2011;29:257-263.
74. Tewari A, Lahmann C, Sarkany R, Bergemann J, Young AR. Human erythema and matrix metalloproteinase-1 mRNA induction, in vivo, share an action spectrum which suggests common chromophores. *Photochem Photobiol Sci*. 2012;11: 216-223.
75. Boyd AS, Naylor M, Cameron GS, et al. The effects of chronic sunscreen use on the histologic changes of dermatoheliosis. *J Am Acad Dermatol*. 1995;33:941-946.
76. Cole C, Appa Y, Ou-Yang H. A broad spectrum high-SPF photostable sunscreen with a high UVA-PF can protect against cellular damage at high UV exposure doses. *Photodermatol Photoimmunol Photomed*. 2014;30:212-219.
77. Hughes MC, Williams GM, Baker P, Green AC. Sunscreen and prevention of skin aging: a randomized trial. *Ann Intern Med*. 2013;158:781-790.