Photoprotection

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Sun exposure is the main cause of photocarcinogenesis, photoageing, and photosensitivity; thus, photoprotection is an important issue. In a skin cancer prevention strategy, behavioural measures—eg, wearing sun protective clothes and a hat and reducing sun exposure to a minimum—should be preferred to sunscreens. Often this solution is deemed to be unacceptable in our global, outdoor society, and sunscreens could become the predominant mode of sun protection for various societal reasons (eg, healthiness of a tan, relaxation in the sun). The application of a liberal quantity of sunscreen has been shown to be by far the most important factor for effectiveness of the sunscreen, followed by the uniformity of application and the specific absorption spectrum of the agent used. The sunscreen market—crowded by numerous products—shows various differences worldwide. Nevertheless, sunscreens should not be abused in an attempt to increase time in the sun to a maximum. Controversies about safety of sunscreens and clinical recommendations are discussed.

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Unprotected exposure to ultraviolet radiation is a major causal factor in the development of skin cancer.[1,2] Non-melanoma skin cancers are initiated for the most part by chronic sunlight exposure and can readily be produced by experimental exposure to ultraviolet radiation in animal models.[3–5] Ultraviolet B (UVB) is the major active terrestrial waveband region that causes direct photochemical damage to DNA, from which gene mutations arise. Unlike UVB, ultraviolet A (UVA) could have more indirect effects on DNA via the generation of reactive oxygen species. The most lethal of the skin cancers, cutaneous malignant melanoma, is more commonly associated with sporadic burning exposure to sunlight—especially early in life—but the wavelengths responsible have not been clearly identified. There are several indications that UVA might have an important role in the pathogenesis of melanoma.[6] However, this involvement has recently been questioned, since only UVB induced melanoma in a transgenic mouse model.[7] There is also mounting evidence that the clinical heterogeneity of malignant melanoma and the variable susceptibility of individuals to its development after exposure to ultraviolet radiation could be explained by specific genetic mutations and polymorphisms, respectively.[8,9]

Ultraviolet radiation also causes skin ageing[10,11] and photodermatoses;[12] responses in human skin vary according to wavelength (table 1).[13] However, the action spectrum for ultraviolet-induced tanning and erythema are almost identical. Indirect evidence suggests that UVA has a greater role in long-term sun damage (figure 1) than it does in acute effects such as sunburn or vitamin D synthesis, which are overwhelmingly attributable to UVB.[14]

To reduce the deleterious effects of ultraviolet radiation to a minimum, public education on photoprotective measures should be promoted continually. In decreasing order of efficacy and lifestyle disruption, we discuss the following measures: complete avoidance of sun exposure, seeking shade at times when disease-inducing wavelengths are relatively intense, wearing clothing protective against ultraviolet radiation penetration, and the use of topical sunscreens to specifically prevent or reduce ultraviolet-induced cellular damage to a minimum.[15]

Environmental photoprotection

Ozone (O_3) is a photoabsorbing molecule present mainly in the stratosphere between 10 and 50 km above the surface of the earth. It absorbs high quantities of shortwave UVB and all ultraviolet C (UVC) radiation, but only a little UVA. The ozone concentration varies naturally according to temperature, weather, latitude, and altitude. The atmosphere is thinner at higher altitudes, resulting in an increase of the intensity of ultraviolet radiation by 4% for every 300 metres of elevation.[16] The average increase in UVB intensity per degree of latitude is about 3%.[16] The time of day also affects the intensity of ultraviolet radiation. At the solar zenith, the sun's rays pass through less of the atmosphere than they do at any other time point; thus, the atmosphere absorbs substantially less ultraviolet radiation. In Denmark, an open prospective observational study showed that 50% of the total daily solar ultraviolet dose reaches the earth between 1200 and 1500h.[17] During the summer, the sun is higher in the sky, and less ultraviolet radiation is absorbed during its passage through the atmosphere.

Substances that deplete ozone (eg, chlorofluorocarbons) have a substantial effect on terrestrial ultraviolet exposure. Although ozone levels vary seasonally, stratospheric ozone levels have decreased annually since the 1970s, especially in the southern hemisphere, and have only recently begun

Search strategy and selection criteria

Data for this Review were selected by searches of Medline with the keywords "sunscreen", "photoprotection", and "sun protection" from 1990 to August, 2006. Articles published in English, French, and German were included. Special focus was placed on work published within the past 3 years. In addition, articles were searched through Scopus from 1998 to the present and without language restriction with the term "sunprotection". The 200 most cited articles from a key reference[65] were searched with Scopus. Several review articles or book chapters were included because they provide comprehensive overviews that are beyond the scope of this Review.

	Acute effect	Chronic effect
190–280 nm (UVC)	Filtered by ozone layer in the stratosphere	NA
280–320 nm (UVB)	Erythema (peak after 8–24 h) Oedema Pigment darkening Delayed tanning Thickening of epidermis and dermis Synthesis of vitamin D	Photocarcinogenesis Immunosuppression Photoageing
320–400 nm (UVA)	Immediate pigment darkening (disappears within 2 h)	Photoageing Immunosuppression Photocarcinogenesis (weak)

Table 1: **Ultraviolet wavelength and effects on human skin**

to stabilise.[18] Sunburn and photosensitivity could have increased in parts of the world after ozone depletion, and it has been estimated that a 1% decrease in ozone levels is followed by a 1–2% increase in melanoma mortality.[18–20]

Fog, haze, clouds, and pollutants can reduce ultraviolet levels by 10–90%. Snow, sand, and metal can reflect up to 90% of ultraviolet. Sea water can reflect up to 15%,[21] whereas little reflection occurs on still water (eg, a pool). Swimmers are potentially exposed to substantial ultraviolet radiation, since penetration through water to a depth of 1 m is possible. Shade alone reduces solar ultraviolet radiation by 50–95%. The amount of protection varies considerably between different shade settings, with a beach umbrella showing the least and dense foliage the most protection.[22] The best technique for reducing ultraviolet exposure is to avoid the sun, especially in the middle of the day.[17]

Photoprotective clothing

During the past two decades, it has been recognised that textiles are a reliable means of photoprotection. Australia has had a leading role in establishing skin cancer education programmes that have urged the use of clothing in conjugation with hats and sunscreens for ultraviolet protection. Nevertheless, several studies have shown that, by contrast with popular opinion, some textiles provide only limited ultraviolet protection.[23–25] Wright and colleagues[24] reported that the protection afforded by a light-coloured cotton shirt was equivalent to a sun-protection factor (SPF; panel 1) of only 10. A third of commercial summer clothing items provide an ultraviolet protection factor (UPF, a measure of total ultraviolet blocked, both UVB and UVA) of less than 12–15.[25]

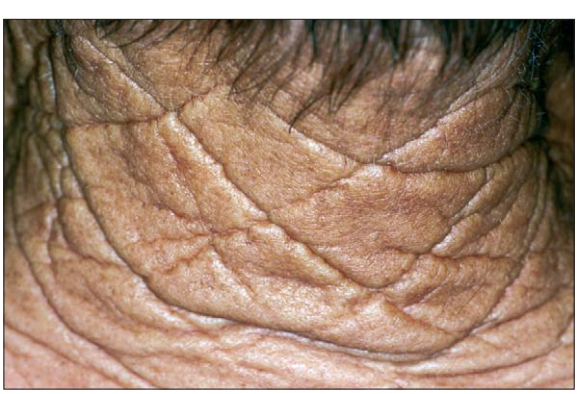

Figure 1: **Extensive nuchal elastosis as a consequence of decades of sun exposure**

Panel 1: Sun protection factor

The sun protection factor (SPF) is a widely accepted method of measuring sunscreen efficacy. SPF is defined as the sun radiation dose (mainly UVB) required to produce the minimum erythemal dose (MED; the threshold dose that can produce sunburn) after application of 2 mg/cm² of sunscreen divided by the dose producing 1 MED on unprotected skin. Thus an SPF of 2 absorbs 50% of ultraviolet radiation, SPF 8 sunscreen can filter out 87·5% of UVB radiation, SPF 16 93·6%, SPF 32 96·9%, and SPF 64 98·4%.[26]

Although there is a recognised way of measuring protection from UVB, there is not a standardised method to measure the efficacy of UVA blocking.[14] The Australian/New Zealand Standard, which has been in use since 1983, is based on in-vitro testing.[27] This standard specifies that a "broad spectrum" claim can be made if the product fulfills one of the following criteria: either an 8-μm layer of the product does not transmit more than 10% of radiation between 320 and 360 nm or an 20-μm layer of the product does not transmit more than 1% of radiation between 320 and 360 nm. In addition to its use in Australia and New Zealand, this standard has been adopted in many European countries. Commonly used in-vivo methods are immediate pigment darkening,[28] persistent pigment darkening,[29,30] and the protection factor test method.[31] Persistent pigment darkening is more reliable than immediate pigment darkening because pigmentation remains stable for 2–24 hours.

Worldwide, there exists a variety of different methods and standards for labelling ultraviolet-protective textiles[32–36] but none are mandatory for manufacturers, leaving the general public uneducated and able only to guess the best means of protection from the sun. Assessment of ultraviolet transmission measured by spectrophotometric methods seems to be more suitable than in-vivo methods.[36–38] To fulfill the protective properties advocated by the Australian/New Zealand standard, the UPF must be greater than 15,[35] whereas UPF should be greater than 40 and average UVA transmission lower than 5% according the European Committee for Standardisation.[39] There is no mandatory standard for photoprotective clothing in the USA at present. Recently, a UPF of 40 or more was recommended as sufficient for extreme exposures in every geographical location and also was adequate to resist against UPF-decreasing effects (eg, stretch, wetness).[32]

Laboratory testing of ultraviolet transmission through fabrics showed that a large number of factors affect transmission—eg, in decreasing order of effect, fabric porosity, type, colour, weight, and thickness (panel 2). Use of clothing that blocks ultraviolet radiation provides

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excellent protection against the hazards of solar radiation, especially garments specifically manufactured to be ultraviolet protective. There are conflicting reports as to whether clothing can prevent melanocytic nevi,[47–49] known to be a strong predictor of risk of subsequent cutaneous malignant melanoma.[50] No effect was seen in adolescent twin study from the UK,[48] whereas a recent analysis in Germany showed a protective effect of clothing in children.[47] These results suggest that everyday clothing is protective, whereas shirts worn on the beach might not offer the same protection as everyday clothing or that the wearing of such items is unreliably reported.[48]

Sunscreens

Several studies have shown a reduction in the number of actinic keratoses[51–53] and squamous cell carcinomas,[54] but not basal cell carcinomas,[54] in careful and regular sunscreen users. Also, mathematical models based on a 3-year, randomised controlled trial of sunscreen use in children showed a 30–40% reduction in new nevi for users of SPF 30 sunscreen compared with control individuals who used the vehicle only.[55] Sunscreen use has recently been shown to attenuate new nevus development on intermittently sun-exposed body sites for white school children, especially in children with freckles.[56] The density of melanocytic nevi is known to be a strong predictor of the risk of subsequent cutaneous malignant melanoma.[50] Furthermore, prevention of acute effects of exposure to ultraviolet radiation—eg, sunburn and formation of sunburn cells, cutaneous DNA damage, and immunosuppression—has been shown,[57–59] as well as prevention of chronic effects including photoageing.[60] However, a recent systematic review failed to show a beneficial effect in preventing malignant melanomas by sunscreens.[61] Even at the beach, only a few people regularly use sunscreens systematically.[62]

Active ingredients in sunscreens differ considerably worldwide (table 2). Even the maximum allowed concentrations of active agents show variation among national regulatory agencies. The list of permitted ultraviolet filters in cosmetic products in the EU has been updated regularly in the past two decades.[63] Currently, there are 27 different sunscreens listed.[63] 28 different sunscreens are approved in Australia and four additional agents are currently under review.[65] By contrast, only 16 agents are listed in the latest Food and Drug Administration (FDA) monograph in the USA.[64] Since 1978, the FDA has allowed only the addition of avobenzone, zinc oxide, and—in 2006—ecamsule to the list. Regulatory agencies in Europe and elsewhere treat sunscreens as cosmetics, where the regulatory approval process is faster. In the USA, sunscreen active ingredients are treated like drugs.

Historical aspects of the development of sunscreens have been reviewed recently.[66] The most successful of the early 20th century sunscreens was certainly Ambre Solaire, containing benzyl salicylate, prepared by Eugene Schueller in 1935. Shortly afterwards Delial, containing benzylimidazole sulfonic acid, was introduced.[66]

Today, topical sunscreens are divided into two broad categories: organic (formerly designated chemical) and inorganic (formerly designated physical) agents.

Panel 2: **Factors that influence ultraviolet protection of clothing**

Factors that increase protection
Tightly woven fibres
Thicker fabrics
Denim, wool, synthetic materials (eg, polyester)[40]
Lax materials
Dry materials
Shrinking after washing[41]
Treatment with a broad-spectrum ultraviolet absorber (eg, Tinosorb)[36,42,43]
Dark-colour fabrics
Unbleached fabrics

Factors that offer lower levels of protection
Loosely woven fibres[40]
Thinner fabrics[44]
Cotton, linen, acetate, rayon[25]
Stretched textiles[45]
Wet materials[42,46]
Hydration[42]
Water washing alone[41]
Light colour fabric[25]
Bleached fabrics

Inorganic agents

Inorganic agents (titanium dioxide and zinc oxide) reflect and scatter ultraviolet and visible radiation from a film of inert metal particles, which forms an opaque barrier. Depending on the particle size, they protect against ultraviolet radiation by both reflection and absorption. They are photostable, do not react with organic sunscreens,[67] and, because of their light scattering properties, there is less variability in the photoprotective effect of inorganic agents when compared with organic sunscreens. Opaque inorganic sunscreens might give some protection against visible light-induced photosensitivity diseases[68] and there are currently no documented reports of sensitisation reactions.

However, inorganic sunscreens are often cosmetically unacceptable because of their opaque quality and occlusiveness. The higher refractive index of titanium dioxide compared with zinc oxide (2·6 *vs* 1·9) explains its whiter appearance and therefore the lower cosmetic acceptability.[67] Recently, modern pharmaceutical approaches such as micronisation and encapsulation have allowed the development of high-quality inorganic sunscreens. Decreasing particle size to 10–50 nm (micronised form) results in less scattering of visible light, leading to a more cosmetically acceptable product.

	Synonyms, abbreviations, and trade names	Maximum concentration	Permitted in
UVB filters			
PABA derivatives			
4-Aminobenzoic acid	PABA	5%,* 15%†‡	EC, USA, AUS
Padimate O	2-Ethylhexyl 4-dimethylaminobenzoate, octyldimethyl PABA, ED-PABA (OD-PABA)	8%	EC, USA, AUS
Ethoxylated ethyl 4-benzoic acid	PEG-PABA, Uvinul P25, Unipabol U17	10%	EC, AUS
2,4,6-Trianilino-(p-carbo-2′-ethylhexyl-1′-oxy)-1,3,5-triazine	Octyl triazone,ethylhexyl triazone, ET, Uvinul T150	5%	EC, AUS
Cinnamates			
Ethylhexyl methoxycinnamate	Octyl methoxycinnamate, EMC, (OMC), Escalol 557, Eusolex 2292, Neo Heliopan AV, Parsol, MCX	7·5†–10%*‡	EC, USA, AUS
Cinoxate	2-Ethoxyethyl p-methoxycinnamate	3†–6%‡	USA, AUS
Isopentenyl-4-methoxycinnamate	Isoamyl 4-methoxycinnamate, IMC, Neo Heliopan E1000	10%	EC, AUS
Salicylates			
2-Ethylhexyl salicylate	Octyl salicylate, octisalate, ES, (OS), Escalol 587, Neo Helipan OS	5%	EC, USA, AUS
Homosalate	Homomethyl salicylate, HMS	10*–15%†‡	EC, USA, AUS
Trolamine salicylate	Triethanolamine salicylate	12%	USA, AUS
Camphors			
Benzylidene camphor sulfonic acid	BCSA, Mexoryl SD-20, Unisol-S22	6%	EC
Polymer of N-[(2 and 4)-[(2-oxoborn-3-ylidene) methyl] benzyl] acrylamide	Polyacrylamidomethyl benzylidene camphor, PBC, Mexoryl SW	6%	EC
N,N,N-Trimethyl-4-(2-oxoborn-3-ylidenemethyl)anilinium methyl sulphate	Camphor benzalkonium methosulfate, CBM, Mexoryl SK	6%	EC, AUS
3-(4′-Methylbenzylidene)-d-1 camphor	4-Methylbenzylidene camphor, MBC, Eusolex 6300, Neo Helipan MBC	4%	EC, AUS
3-Benzylidene camphor	3-Benzylidene camphor, BC, Mexoryl SD-20, Unisol-S-22	2%	EC
Others			
2-cyano-3,3-diphenyl acrylic acid	2-ethyl hexyl ester, octocrylene, 2-ethylhexyl-2-cyano-3,3 diphenylacrylate, Eusolex OCR, Neo Helipan 303	10%	EC, USA, AUS
2-Phenylbenzimidazole-5-sulfonic acid and its potassium, sodium and triethanolamine salts	Phenylbenzimidazole sulfonic acid, PBSA, ensulizole, Eusolex 232, Neo Heliopan Hydro, Parsol HS	4†‡–8%*	EC, USA, AUS
UVA filters			
Benzophenones			
Benzophenone-3§	Oxybenzone, BENZ-3, Eusolex 4360, Neo Helipan BB, Uvinul M40, Escalol 567, UVAsorb MET/C	6†–10%*‡	EC, USA, AUS
2-Hydroxy-4-methoxybenzophenone-5-sulfonic acid§	Sulisobenzone, BENZ-4, UVAsorb S5, Escalol 577, Uvinul MS 40	5*–10%†‡	EC, USA, AUS
2-Hydroxy-4-methoxybenzophenone-5-sulfonic sodium salt§	Benzophenone-5, BENZ-5, sulisobenzone sodium	5*–10%†‡	EC, USA, AUS
Dioxybenzone	Benzophenone-8	3%	USA, AUS
Others			
Menthyl anthranilate	Methyl-2-aminobenzoate, meradimate	5%	USA, AUS
1-(4-tert-butylphenyl)-3(4-methoxyphenyl)propane-1,3-dione	Butyl methoxy dibenzoylmethane, avobenzone, BMDBM, Parsol 1789, Eusolex 9020	3†–5%*‡	EC, USA, AUS
2,2′-Methylene-bis-6-(2H-benzotriazol-2yl)-4-(tetramethyl-butyl)-1,1,3,3-phenol§	Methylene bis-benzotriazolyl tetramethylbutylphenol, MBBT, Tinosorb M	10%	EC, AUS
Phenol,2-(2H-benzotriazol-2-yl)-4-methyl-6[2-methyl-3-[1,3,3,3-tetramethyl-1-[(trimethylsilyl)oxy]disiloxanyl]propyl§	Drometrizole trisiloxane, DTS, Mexoryl XL	15%	EC, AUS
2,2′-(1,4-Phenylene)bis-(1-H-benzimidazole-4,6-disulfonic acid, monosodium salt§	Disodium phenyl dibenzimidazole tetrasulfonate, bisimidazylate, DPDT, Neoheliopan AP	10%	EC, AUS
Terephthalylidene dicamphor sulfonic acid	Ecamsule, TDSA, Mexoryl SX	10%	EC, USA¶, AUS
4,4-((6-(((1,1-dimethylethyl)amino)carbonyl)phenyl)amino)-1,3,5-triazine-2,4-diyl)diimino)bis-,bis(2-ethylhexyl)ester)	Diethylhexyl butamido triazone, DBT, UVAsorb HEB	10%	EC
Dimethico-diethylbenzalmalonate§	DDBM, Parsol SLX	10%	EC, AUS
(1,3,5)-Triazine-2,4-bis((4-(2-ethyl-hexyloxy)-2-hydroxy)-phenyl)-6-(4-methoxyphenyl)§	Bis-ethylhexyloxyphenol methoxyphenol triazine, bemotrizinol, BEMT, Tinosorb S	10%	EC, AUS
Inorganic absorbers			
Titanium dioxide§ **[Au: OK?]**		25%	EC, USA, AUS
Zinc oxide§ **[Au: OK?]**		25%† — no limit‡	EC, USA, AUS (not explicitly listed in ref 63)

EC=European Community, AUS=Australia. *List of permitted ultraviolet filters in the Council Directive of the European Committee.[63] †Ultraviolet filters listed in the US Food and Drug Administration monograph.[64] ‡Ultraviolet filters listed in the Australian regulatory guidelines for over-the-counter medicines (ARGOM) by the Therapeutic Goods Administration, Aug 18, 2006.[65] ¶Approved July 21, 2006. §UVA and UVB filter.

Table 2: **Sunscreen agents permitted as active ingredients in listed products in Australia, the European Committee (EC), and the USA (Food and Drug Administration monograph)**

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Micronisation shifts the protective spectrum, via its property as an absorbing agent, towards shorter wavelengths.[69] Microfine titanium dioxide and zinc oxide have been found to be highly protective against harmful ultraviolet rays[67,70] and offer good protection against short-term UVB-induced immunomodulation in human trials.[71]

Neither zinc oxide nor titanium dioxide have relevant skin irritating properties and sensitisation potential in human beings.[72] Concerns related to the penetration of inorganic agents into the skin have been discussed, but in-vivo and in-vitro studies found no evidence of penetration of titanium dioxide and limited penetration only for zinc oxide, which is slightly soluble.[72] Serum concentrations of zinc oxide after whole-body application were unchanged, and in-vitro studies have shown no penetration beyond the stratum corneum.[72] Simple washing procedures are sufficient to remove microfine titanium dioxide from the skin.[73] Microfine titanium dioxide has an absorption profile greater in UVB than does microfine zinc oxide; by contrast, zinc oxide was found to be more effective in UVA protection (up to 380 nm) than was microfine titanium dioxide.[74] These effects vary largely due to the particle size of the substances. Microparticles tend to agglomerate and aggregate due to electrostatic effects, resulting in potentially greater loss in efficacy. Therefore, the micropigments have to be coated and kept in dispersion, which is still a major challenge for the cosmetic industry.[75]

Sunscreens containing inorganic agents alone are generally recommended for children, because of their lack of penetration and subsequent degradation in the body,[76] absence of photo-related effects (ie, photoallergy), and no evidence of photogenotoxicity in vivo.[72]

Organic agents

Organic sunscreens act by absorbing ultraviolet radiation. Ultraviolet radiation activates the agent's electrons from the passive to an excited state. When returning to the stable condition, energy is emitted as insignificant quantities of warmth or fluorescent radiation.

These agents are broadly divided into UVB, UVA, or broadband absorbers. To be effective, the filter should be stable photochemically in sunlight, dissolve or disperse easily and permanently in the vehicle, and remain in place after perspiration or swimming. Additionally, the agent should be non-toxic and not cause irritation or contact allergy. UVB absorbers have been commonly used worldwide for decades (table 2), whereas most UVA and broadband absorbers have been developed in recent years. Since a sunscreen has to protect against the entire ultraviolet spectrum, different filters have to be combined in the same product.[69] The cinnamates (mostly 2-ethyl *p*-methoxycinnamate; EMC) are by far the most popular UVB absorbers in the USA and Europe,[69,77] and are used in combination with other UVB absorbers to achieve a high SPF. The second most popular filters in Europe during the recent past are the camphor derivatives.[69] Salicylates and para-aminobenzoic acid (PABA) and its derivatives are among the oldest commercially available UVB filters and are still used worldwide.

The increasing need for broadband agents and improved photostability has led to the introduction of a new generation of filters, including methylene bis-benzotriazolyl tetramethylbutylphenol (Tinosorb M) and bis-ethylhexyloxyphenol methoxyphenol triazine (Tinosorb S), both manufactured by Ciba Specialty Chemicals (Basel, Switzerland), as well as terephthalylidene dicamphor sulfonic acid (Mexoryl SX) and drometrizol trisiloxane (Mexoryl XL), produced by L'Oréal (Clichy, France). Mexoryl SX is a photostable broad-spectrum absorber and Mexoryl XL can absorb both UVB and UVA. Both protect against induction of pigmentation and show a synergistic effect when used in combination.[78] Tinosorb S is an oil-soluble, highly photostable broad-spectrum ultraviolet filter with a good absortion in the UVA range, which can be used successfully to improve the photostability and efficiency of sunscreens containing avobenzone and EMC.[79] Tinosorb M consists of microfine organic particles that are dispersed in the aqueous phase of the sunscreen emulsion, thus combining the benefits of an organic filter with those of an inorganic filter. Because tinosorb molecules are large, they are less likely to be absorbed through the skin. Absence of endocrine activity has been shown in vitro.[80] The mexoryls and tinosorbs are not licensed in the USA and Japan. In Europe, the list of permitted ultraviolet filters recognised by the Council Directive of the European Committee[63] has been regularly questioned. Currently five sunscreen agents are under review: benzophenone-3, camphor benzalkonium methosulfate, homosalate, PABA, and phenylbenzimidazole sulfonic acid.

The self-tanning product dihydroxyacetone has generally not been considered to provide sun protection. However, there is some evidence to suggest that it gives some protection, with an SPF of 2–3 and a durability of 5–6 days.[81,82] The protective nature of the compound has been confirmed in a hairless mouse study that showed a delay of broad-spectrum ultraviolet carcinogenesis;[83] the compound could therefore function as a base for other protection measures.

Organic and inorganic ultraviolet filter substances have been shown to act synergistically to increase the SPF.[84] Inorganic agents increase the optical pathway of the photons in the topically applied absorbing formulation. In this way, more photons are absorbed, increasing the SPF.[84]

Controversies of sunscreens

Recent controversy surrounding sunscreen efficacy[85] and safety[86,87] has stimulated a reassessment of their use and properties.

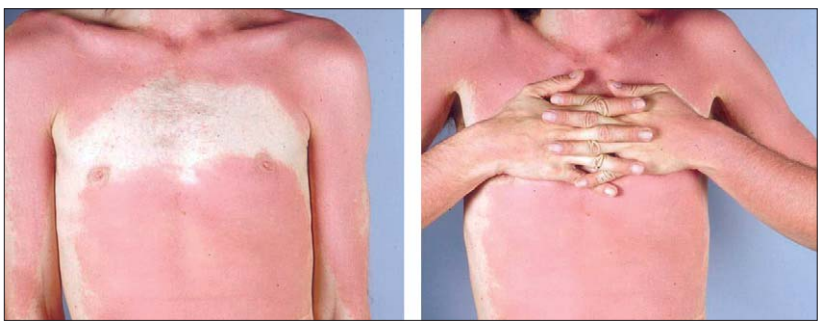

Figure 2: **Inadequate sun protection resulting in sunburn as a consequence of sleeping in the sun**

Efficacy

In terms of acute ultraviolet damage, actinic keratoses, and non-melanoma skin cancer, studies have shown a direct protective effect of sunscreen use in human beings.[52,54,57–59,88] However, several studies have suggested that the use of sunscreens might be associated with increased nevus density,[89,90] a strong predictor of risk of subsequent melanoma.[50,91] These retrospective studies could have several shortcomings in controlling for the confounding effects of phenotype, prior sun exposure, and frequency of sunscreen use.[62] A recent randomised controlled study in children showed attenuated new nevus development on intermittently sun-exposed body sites for white school children in Vancouver, Canada.[56] However, whether sunscreens can reduce the risk for melanoma has not yet been proven definitively. A case-control study from southern Sweden of 571 patients with a first diagnosis of cutaneous malignant melanoma showed a significantly raised odds ratio for developing malignant melanoma after regular sunscreen use (odds ratio 1·8, 95% CI 1·1–2·9).[85] A systematic review by Dennis and colleagues[61] that examined 18 heterogeneous case-control studies failed to show any association between melanoma and sunscreen use. Different factors must be taken in to account to explain the actual lack of proof of preventive effects. First, the median SPF of commonly used sunscreens before the early 1990s was 4–10, and these sunscreens incorporated active ultraviolet filters that were limited largely to the UVB waveband.[92] Only by 1997 had median SPF risen to about 15.[92] Second, higher protection has been anticipated to induce longer sun exposure by postponing warning signs such as sunburn, or by providing a false impression of safety in the sun. In this regard, two randomised trials in students during their holidays have shown that application of a high SPF prompted them to increase the duration of their sun exposure.[93,94] A recent prospective study by Thieden and colleagues[62] has shown that people use sunscreen when they know they are going to stay out for a long time and thus apply sunscreen as a tanning aid to avoid sunburn.[95,96] Third, failure to apply sunscreen properly must be emphasised: sunscreens are frequently not applied before exposure[97] or early after onset of exposure.[98] Additionally, the SPF of a sunscreen is assessed after phototesting in vivo at an internationally agreed application thickness of 2 mg/cm^2.[64,99] Several studies have shown that consumers apply much less than this, achieving only 10–25% of the protection expected from the product label.[100,101] The uniformity of sunscreen application, failure to apply to all exposed skin, resistance to water immersion, and the number of applications per day are known to influence protection.[102] Considering these factors, Diffey[103] concludes that it is not surprising that case-control studies have failed to find any association between the use of sunscreens and the risk of melanoma, especially with such a limited effect of older sunscreens on modifying solar ultraviolet exposure. Therefore, to anticipate that newer formulations of sunscreens will lead to a benefit as a protective agent against melanoma is reasonable, although such a benefit might not be seen for several decades.[103] However, their use in practice could be difficult, time consuming, and expensive, and they can, in general, be used only in addition to the more reliable measures of clothing protection and reduction of ultraviolet exposure during peak hours of solar radiation.

Safety

Adverse reactions from sunscreen ingredients—including allergic and irritant contact dermatitis, phototoxic and photoallergic reactions, contact urticaria, and even solitary cases of severe anaphylactic reactions—have been increasingly reported.[88,104,105] Adverse reactions to sunscreens have been shown to occur in as many as 19% of individuals in one Australian study.[106] Most of these adverse reactions were due to irritant rather than allergic reactions to either the sunscreen agents or the base. The prevalence of allergy to sunscreens in the general population is not known, but recent photopatch test results showed a low yield of positive reactions.[107] Thus, despite the large increase in the use of ultraviolet filters over the past decade, the development of photoallergic reactions remains rare. Furthermore, most of the common ultraviolet filter photoallergens, including PABA, amyl dimethyl PABA, and benzophenone-10, are now rarely used in sunscreen manufacture; isopropyl dibenzoylmethane was voluntarily removed from the market in 1993.[107] Currently, benzophenone-3 (a UVA filter) is the most common contact photoallergen still in widespread use.[104,107] Other UVA filters—eg, avobenzone (Parsol 1789) and sulisobenzone (benzophenone-4)—and the UVB filters methylbenzylidene camphor, octyl methoxycinnamate, and ensulizole, are known to rarely induce contact allergic and photoallergic reactions. However, there is currently no evidence that allergic reactions represent a common clinical problem. Nevertheless, patients with photodermatoses such as polymorphous light eruption and chronic actinic dermatitis represent a group of patients at increased risk of developing photoallergy.

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Gasparro and colleagues[108] reviewed in-vitro and in-vivo studies of cytotoxicity and photogenotoxicity of sunscreens. Concerns from in-vitro studies that showed direct or indirect interactions from sunscreens—mainly PABA and its derivatives—with DNA following exposure to ultraviolet radiation[108–110] could not be confirmed in vivo.[108,111,112] Collectively, data from in-vivo studies seem to diminish, if not eliminate, photocarcinogenicity concerns, since sunscreens delay photocarcinogenesis in hairless mice.[113] However, further in-vivo and in-vitro studies are needed to clarify mechanisms of immunosuppression, DNA repair, and mutagenesis.

Since sunscreens are increasingly included in diverse consumer products, questions regarding their long-term safety have been raised. 90% of all requisite vitamin D is formed within the skin through the action of ultraviolet radiation. Several studies have suggested a connection between vitamin D deficiency and over a dozen forms of cancer (eg, colon, breast, prostate)[114,115] and recently also for malignant melanoma.[116] Berwick and colleagues[117] noted that subsequent mortality from melanoma was about half as high in those with signs of solar elastosis (assessed by means of a standardised physical examination) as in those without solar elastosis, indicating a possible link to vitamin D levels. These results should be interpreted cautiously since continued sun exposure would increase the risk of a second melanoma as well as squamous cell carcinoma. For 2004, the US economic burden due to vitamin D insufficiency from inadequate exposure to solar UVB irradiance, diet, and supplements is estimated to be $40–56 billion, whereas that for excess ultraviolet irradiance is estimated to be $6–7 billion;[118] further research is required to confirm these estimates. However, clinical studies have shown that long-term use of sunscreen had little or no effect on vitamin D levels, and did not induce osteoporosis or secondary hyperparathyroidism.[119,120] Only low levels of exposure to ultraviolet radiation are necessary to avoid vitamin D deficiency. Exposure of the hands, arms, and face two to three times a week to a third to a half of minimum erythemal dose (about 5 min for a skin type 2 adult in Boston at noon in July; panel 1) in the spring, summer, and autumn is more than adequate.[121]

There are also concerns about the endocrine effect of ultraviolet filters. Five chemicals—benzophenone-3, homosalate, 4-methyl-benzylidene camphor, octyl-methoxycinnamate, and octyl-dimethyl-PABA—increased breast cancer cell proliferation in vitro,[86] whereas butyl-methoxydibenzoylmethane was inactive. Oral application of 4-methylbenzilidene camphor and octyl-methoxy-cinnamate, and to a lesser degree benzophenone-3, increased uterine weight of immature Long-Evans rats. Dermal application of 4-methylbenzilidene camphor to immature hairless rats also increased uterine weight. Further data indicated that the ultraviolet filters benzophenone-3 and homosalate possess antiandrogenic activity in vitro[122] in addition to oestrogenic activity. Thus, the conclusion was reached that daily exposure to sunscreen formulations might have oestrogenic effects in human beings.[123] Questions have been raised about the methodological grounds used.[124] In the animal experiments, topical exposure to ultraviolet filters was judged to be unrealistically high compared with potential human exposure scenarios. Furthermore, a study on 32 people, who had a sunscreen containing benzophenone-3, octyl-methoxycinnamate, and 3-(4-methylbenzilidene) applied to their whole body daily for 5 days did show uptake in the body but no effects on reproductive hormone levels.[76] Therefore the biological relevance of the oestrogenic effect of the tested ultraviolet filters has not been established and additional long-term studies are required.

Clinical recommendations

In a skin cancer prevention strategy, behavioural measures—eg, wearing sun protective clothes and a hat and reducing sun exposure to a minimum—must be preferred to sunscreens. For improved protection, especially if midday summer exposure or tropical exposure is unavoidable, the use of clothing over as much of the skin surface as possible,[42] and proper application of a highly protective sunscreen over the remainder of the exposed skin, is very effective. Since sun protection practices, especially in the western world, are still inadequate (figure 2) and since sunscreens will be used by many as the predominant mode of sun protection for various societal reasons (eg, healthiness of a tan, relaxation

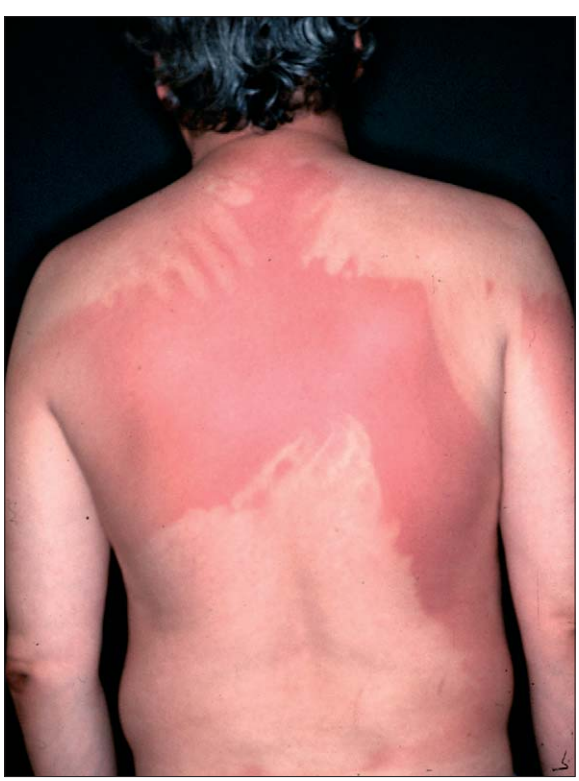

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Figure 3: Solar erythema shows the lack of uniformity of sunscreen application

in the sun), the population has to be advised as to how to make the best use of sunscreens.[125] The application of a liberal quantity of sunscreen is by far the most important factor for effectiveness of the sunscreen, followed by the uniformity of application (figure 3) and the specific absorption spectrum of the agent used.[101] Application of organic sunscreens to exposed sites should be done 15–30 minutes before going out into the sun. Waterproof or water-resistant sunscreens should be used to diminish the need for reapplication after swimming followed by towelling, friction with clothing or sand, and sweating. Although the better protection against UVB that is provided by high SPF sunscreens (SPF >15) has not been clearly proven to further protect against skin cancer, the overall data has shown that a high SPF is preferable to low SPF sunscreen.[96] Broad-spectrum sunscreens with adequate UVA protection should be used, but there is no clear definition of what is deemed to be adequate. Nevertheless, sunscreens should not be abused in an attempt to increase time in the sun to a maximum. The year-round daily use of sunscreen for people living in countries of low insolation—eg, the UK and northern Europe—can not be recommended, and sunscreens are best avoided during October to March.[126] There is some evidence to suggest that the year-round application of sunscreens can be beneficial in terms of prevention of cancer and solar elastosis in areas of high insolation, such as Queensland, Australia, and Texas, USA.[54,127]

Conflict of interest statement

We declare that we have no conflict of interest.

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