Current sunscreen issues: 2007 Food and Drug Administration sunscreen labelling recommendations and combination sunscreen/insect repellent products

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The Food and Drug Administration (FDA) regulates sunscreens as over-the-counter drugs. This article describes sunscreen actives available in the United States, new developments available elsewhere, and the amendment to the FDA 1999 sunscreen monograph, released on August 27, 2007, which proposes a new grading system for ultraviolet B protection, a cap of the sunburn protection factor to 50+, and a 4-star grading of ultraviolet A protection. In addition, current data on combination sunscreen and insect repellent products are discussed. Application of a combination product too frequently poses the risk of insect repellent toxicity, whereas application too infrequently invites photodamage. It may be prudent to follow the same approach of our Canadian colleagues of discontinuing combination products until more investigations are available. (J Am Acad Dermatol 2008;59:316-23.)

SUNSCREENS

In the United States, the Food and Drug Administration (FDA) regulates sunscreens as over-the-counter drugs, establishing the conditions under which these products are recognized as safe and effective for photoprotection.[1,2] In the FDA monograph, the term "sunscreen drugs" is used to refer to sunscreen actives or ultraviolet (UV) filters. Currently there are two procedures for registering and obtaining FDA approval for sunscreen drugs: New Drug Application and the Time and Extent Application (TEA). The FDA introduced the TEA in 2002 as a faster and less costly alternative to a New Drug Application. To be considered for TEA, a minimum of 5 years of over-the-counter marketing of the product in the same country is required; data generated from that country can then be submitted to the FDA for consideration.[3] The latest version of the FDA sunscreen monograph was issued in 1999 with a list of 16 approved sunscreen drugs, their approved maximum concentrations (Table I), labeling requirements, and testing procedures.[1] The FDA proposed that all 16 sunscreen drugs be classified as either inorganic or organic, replacing the terms "physical" or "chemical" sunscreen drugs, respectively.[1,2] Comments from the American Academy of Dermatology (AAD) on the 1999 monograph were submitted to the FDA in 1999, during the 90-day comments period, after an AAD-sponsored consensus conference; the comments included the suggestion of establishing UVA protection methods that can be conveyed clearly to the general public.[4]

There are 3 commonly used nomenclatures for UV sunscreen actives in the world.[5] In many countries, the International Nomenclature Cosmetic Ingredient nomenclature is used. In the United States, the US Adopted Name is used by the FDA, and trade names are also commonly used. These nomenclatures, using two widely used UVA filters, oxybenzone and avobenzone, as examples, are illustrated in Table II.

Abbreviations used:

AAD:	American Academy of Dermatology
DEET:	n,n-diethyl-meta-toluamide
FDA:	Food and Drug Administration
SPF:	sun protection factor
TEA:	Time and Extent Application
UV:	ultraviolet

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Table I. Sunscreen drugs and maximum approved concentrations listed in the 1999 Food and Drug Administration sunscreen monograph

Sunscreen drugs	Maximum approved concentration	Comments
Inorganic		
Titanium dioxide	25%	Both commonly used in microfine form; scatter visible light and UV light, and absorb UV light
Zinc oxide	25%	
Organic		
UVB		
PABA	15%	Common cause of contact and photocontact allergy; no longer commonly used
Padimate O	8%	Most commonly used PABA derivative
Octinoxate	7.5%	Most commonly used UVB filter; photolabile
Cinoxate	3%	A cinnamate derivative
Octisalate	5%	These 3 salicylate derivatives are weak UV absorbers; photostable; trolamine salicylate is water soluble
Homosalate	15%	
Trolamine salicylate	12%	
Octocrylene	10%	Photostable
Ensulizole	4%	Water soluble
UVA		
Oxybenzone	6%	These benzophenone derivates have absorption peaks at the UVB and UVA2 range; oxybenzone is the most common cause of photoallergic contact dermatitis to UV filters; photostable
Sulisobenzone	10%	
Dioxybenzone	3%	
Avobenzone	3%	The only approved UVA filter with absorption peak at UVA1 (357 nm); photounstable
Meradimate	5%	UVA2 filter

All listed as United States Adopted Name.
PABA, Para-aminobenzoic acid; *UV*, ultraviolet.

Table II. Examples of the 2 sunscreen drug nomenclatures: US Adopted Name, trade name, and International Nomenclature Cosmetic Ingredient

USAN	Trade names[5]	INCI
Oxybenzone	>20 Trade names	Benzophenone-3
Avobenzone	Escalol 517, Eusolex 9020; Neo Heliopan 357; Parsol 1789; Solarom BMBM	Butyl methoxydibenzoylmethane

INCI, International Nomenclature Cosmetic Ingredient; *USAN*, US Adopted Name.

Newly included agents in the 1999 monograph are avobenzone (butyl methoxydibenzoylmethane, Parsol 1789) and zinc oxide.[2] Furthermore, several broad-spectrum sunscreen products containing ecamsule (terephtalydene dicamphor sulfonic acid, Mexoryl SX) were recently approved by the FDA, the first one in July 2006.[6] Ecamsule in these products was approved as an ingredient of the final products, rather than an individual UV sunscreen drug, through the New Drug Application process. For this reason, ecamsule is not listed among the approved sunscreen drugs.

The European Union, Japan, South America, and South Africa regulate sunscreens as over-the-counter cosmetic products, allowing approval process within 1 to 2 years after application. For these over-the-counter sunscreen cosmetics, toxicologic studies are generally required for application including effects on fertility; embryofetal, perinatal, and postnatal toxicity; in vitro and in vivo toxicity; genetics; carcinogenicity; and acute and chronic toxicity.[3]

Inorganic filters

Inorganic (previously called "physical") sunscreen drugs are photostable UV sunscreen drugs that protect against UV radiation by reflecting, scattering, or absorbing UV, depending on the particle size. Thick coating is necessary to achieve sufficient degree of reflection, therefore, opaque inorganic

Table III. Agents that photostabilize avobenzone

UVB filters
Enzacamene*
Homosalate
Octisalate
Octocrylene
UVA filter
Oxybenzone
Broad-spectrum UVB-UVA filters
Bemotrizinol*
Titanium dioxide (microfine)
Zinc oxide (microfine)
Others
Diethylhexyl 2,6-naphthalate
Diethylhexyl syringylidene malonate

All UV filters are listed as US Adopted Name.
UV, Ultraviolet.
*Not approved by the Food and Drug Administration, used in other parts of the world.

sunscreen actives protect against visible light-induced photosensitivity. On the other hand, decreasing the particle size into the micronized or ultrafine form considerably improves cosmetic acceptability by lessening the scattering of visible light; it also shifts the protection toward shorter wavelengths and toward absorbency function.

Microfine zinc oxide is a broad-spectrum photostable sunscreen that protects from the UVB to the UVA1 (340-400 nm) range. It is more effective in the UVA protection than microfine titanium dioxide, which is more protective in the UVB and UVA2 (320-340 nm) range. Attenuation is the sum of scattering and absorption; the maximum attenuation peak of inorganic sunscreens depends on their particle size. In one study, it was shown that the attenuation peak for microfine zinc oxide is around 380 nm, and for microfine titanium dioxide is in the 300- to 310-nm range.[7] Furthermore, titanium dioxide has a higher refractive index and is, therefore, whiter, despite a smaller particle size.[2,8]

Because of electrostatic effects, microfine particles of zinc oxide and titanium dioxide tend to aggregate with potential loss in efficacy. Therefore, zinc oxide and titanium dioxide are usually coated with dimethicone or silica to keep these particles in dispersion. In addition, such coatings also markedly decrease the photoreactivity of these particles.[3,7]

Organic UVB filters

FDA-approved UVB sunscreen drugs are listed in Table I.[1,2,5]

Other UVB sunscreen actives approved for use in the European Union and other countries but not currently approved by the FDA include camphor derivates,[2] Uvinil T 150 (ethylhexyl triazone), Uvasorb HEB (diethylhexyl butamido triazone), and Parsol SLX (benxyledene malonate polysiloxane).[3]

Camphor derivatives are moderately effective UVB absorbers with a maximum peak absorption at 300 nm[2].

Univinil T 150 is a UVB sunscreen active with peak absorption at 314 nm that has been available in Europe for several years. Univinil T 150 is composed of a chromophore of para-aminobenzoic acid linked to a triazine ring. Although its solubility is limited, it can be incorporated into sunscreen products in considerable amounts. It was considered to be the best UVB sunscreen active before the introduction of Uvasorb HEB, which has maximum peak absorption at 312 nm, slight improvement in efficacy, and increased solubility compared with Uvinil T 150.

Parsol SLX is a UVB sunscreen active with maximum peak absorption at 312 nm and very large molecular weight[3] (>6000 daltons).[5] Parsol SLX does not penetrate into the skin surface, resulting in improved safety; however, it has very low UV absorbing properties. It is generally used in combination with other products such as avobenzone or inorganic sunscreen drugs, resulting in a broad-spectrum photostable sunscreen.[3]

Organic UVA filters

FDA-approved organic UVA sunscreen drugs are listed in Table I.

Avobenzone, the best long-wave UVA1 filter currently available in the United States, is photounstable; therefore, it is frequently combined with other sunscreens or stabilizers to increase photostability of the final product.[2] Agents that have been used to increase the photostability of the final product are listed in Table III. Ecamsule, recently approved by the FDA as an active ingredient in several sunscreen products, is an intrinsically photostable sunscreen drug that absorbs in the UVA2 range.[3]

Other broad-spectrum and intrinsically photostable UVB and UVA sunscreen actives, not yet available in the United States, include bemotrizinol (anizotriazine, bis-ethylhexyloxyphenol methoxyphenol triazine, Tinosorb S), bisoctrizole (methylene-bis-benzotriazoyl tetramethylbutylphenol, Tinosorb M), and silatriazole (drometriazole trisiloxane, Mexoryl XL)[3]; the first two are currently undergoing the FDA TEA approval process.[2,3] Bisdisulizole disodium (disodium phenyl dibenzimidazole tetrasulfonate, Neo Heliopan AP) and Uvinul A Plus (diethylamino hydroxybenzoyl hexyl benzoate) are also UVA sunscreen actives not available in the United States.[3] With the exception of Uvinul A Plus, all these

new-generation sunscreen products have molecular weight over 500 daltons, hence, minimizing the possibility of percutaneous absorption.

Bemotrizinol is a photostable UVB and UVA sunscreen active with maximum peak absorption at 310 and 343 nm.[2,3] Bisoctrizole is a photostable UVB and UVA sunscreen active with two maximum absorption peaks at 305 and 360 nm. It has both organic and inorganic properties; it consists of microfine particles (100-200 nm) that absorb UV, and that scatter and reflect it. The particles are dispersed in water phase allowing for synergistic effects with oil-soluble sunscreen actives.[3] Both bisoctrizole and bemotrizinol were shown to have no estrogenic or androgenic activities.

Silatriazole is a photostable UVB and UVA sunscreen active with two absorption spectra in the UVB and UVA range (290-320 nm, maximum absorption peaks 303 nm; and 320-360 nm, maximum absorption peaks 344 nm, respectively).[2,3]

Neo Heliopan AP is a water-soluble UVA sunscreen active with maximum peak absorption at 334 nm. Uvinul A Plus has maximum peak absorption at 354 nm and was launched as a successor of avobenzone because of its similar absorptive properties but superior photostability.[3]

Nanotechnology

Nanotechnology is described by the National Institute of Health as "research and technology development at the atomic, molecular or macromolecular level in the dimension range of approximately 1 to 100 nm to provide fundamental understanding of phenomena and materials at the nanoscale and to create and use structures, devices and systems that have novel properties and functions because of their small and/or intermediate size."[9] Sunscreen actives that have undergone this process are zinc oxide, titanium dioxide, and bisoctrizole.

Microfine forms of inorganic sunscreens became available in the early 1990s, with particles sizes of 20 to 50 nm.[7,10] The nanotechnologies were developed for these inorganic sunscreen drugs to allow for a more cosmetically acceptable and transparent final product. Microfine inorganic sunscreens have the advantage of both inorganic (the ability to reflect and scatter UV radiation) and organic (UV absorbing) properties. Inorganic properties decrease with particle size.[3] Nanotechnologies also shift the protection to UVB and shorter wavelength UVA.

Because of the concern that in vitro, nanoparticulate zinc oxide and titanium dioxide can induce free radical formation in the presence of UV, the safety of microfine inorganic particles has been investigated. Gamer et al[11] found no penetration beyond the stratum corneum in vitro on porcine skin using a sunscreen product containing 10% microfine coated titanium dioxide (<60 nm) and microfine uncoated zinc oxide (<160 nm). Pflucker et al[12] reported no penetration beyond the stratum corneum in vivo in human volunteers of 3 sunscreen formulations containing micronized titanium dioxide (10-100 nm). Lademann et al[13] found no penetration of a sunscreen containing titanium dioxide nanoparticles beyond the stratum corneum in human volunteers. In a review of all the studies done on this topic, the Australian Government Therapeutic Goods Administration has concluded that these particles remain on the surface of the skin and in the stratum corneum.[14] Micronized and ultrafine zinc and titanium dioxide are approved and deemed safe by the FDA, and are not considered as new sunscreen drug products, instead, they are considered as a variation in particle size of approved drugs.[1]

Hormonal effects of sunscreens

Recently, reported estrogenic effects of UV filters have raised concern about the long-term safety of sunscreen use. Schlumpf et al[15] investigated estrogenicity of certain sunscreen products, in both in vitro and in vivo animal models. The in vitro experiment consisted of exposure of MCF-7 breast cancer cells to 6 UV filters: oxybenzone, homosalate, enzacamene, octinoxate, padimate O, and avobenzone. With a notable exception of avobenzone, exposure to each of the other 5 filters resulted in increased cell proliferation. The proliferative effect of enzacamene was blocked by an estrogen antagonist. Immature Long-Evans rats were fed with the above 6 chemicals in powdered form; a dose-dependent increase in uterine weight after feeding with enzacamene, with octinoxate, and to a lesser degree, with oxybenzone, was observed. Dermal application of enzacamene to immature hairless rats also increased the uterine weight.[15] An in vitro study by the same group reported antiandrogenic activity of the sunscreen drugs oxybenzone and homosalate by antagonizing dihydrotestosterone-induced androgen receptor activation in the human breast carcinoma cell line MDA-kb2.[2,8,16] A study by Nakagawa and Suzuki[17] reported the in vitro estrogenic effect of certain hydroxylated intermediates of benzophenone in vitro in human breast cancer cells, as assessed by estrogen receptor competitive binding assay.[2]

However, experimental models and techniques of the above studies have been questioned as the doses of sunscreen drug products used were unrealistically large compared with human exposure scenarios. In addition, the dermal application technique has been

considered inappropriate. In fact, the Scientific Committee of Cosmetic Products and Non-Food Products, an European committee based in Belgium, noted that the relative estrogenic potencies of UV sunscreen products, both in vitro and in vivo, were about 1 million less than estradiol, the positive control substance.[2] In human subjects, a study by Janjua et al[18] demonstrated no effects on reproductive hormone levels in 32 individuals after applying oxybenzone, octinoxate, and enzacamene daily for 5 days despite uptake of these sunscreen drugs in the body.

Thus, the endocrine effects of these UV sunscreen actives remain controversial, and the clinical relevance of the estrogenic effects of UV sunscreen actives is still unclear. Further studies, especially in human subjects, are warranted.

2007 proposed amendment to the 1999 FDA sunscreen monograph

An amendment to the 1999 sunscreen monograph was released by the FDA on August 27, 2007.[19] Important aspects of the 2007 amendment include: a cap in the sun protection factor (SPF) to 50+, a proposal of new grading systems for UVB and UVA protection, and several recommendations in directions of use and labeling, including the requirement of a sun alert statement warning. These will be outlined below.

UVB protection requirements. In the 2007 amendment, the acronym "SPF" was proposed to be changed from "sun protection factor" to "UVB sunburn protection factor"; this is to differentiate the biologic effects UVB and UVA, and the different measurements needed to assess these biologic effects. Furthermore, a grading system for UVB sunburn protection factor was proposed based on the following 4 categories: (1) low UVB sunburn protection: sunscreen products with SPF 2 to less than 15; (2) medium UVB sunburn protection: sunscreen products with SPF 15 to less than 30; (3) high UVB sunburn protection: sunscreen products with SPF 30 to 50; and (4) highest UVB sunburn protection: sunscreen products with SPF more than 50.

In addition, the FDA recommends that manufacturers can label their products with the specific SPF values up to, but no greater than, 50; sunscreen drugs with SPF greater than 50 would be labeled as 50+. The rationale for this cap is because the FDA is of the opinion that there are no current data demonstrating the accuracy and reproducibility of specific SPF values over 50. To achieve a SPF50+, products would need to have SPF of 60.

UVA protection requirements. In the 1999 FDA sunscreen monograph, requirements for UVA protection were not addressed. A significant portion of the 2007 amendment to the 1999 sunscreen monograph has been dedicated to UVA protection, with the introduction of a new grading system of the level of UVA protection. The proposed grading system is comprised of a 4-star rating system that ranges from low, medium, high, to highest UVA protection, and is based on both in vivo and in vitro testing procedures.

In vivo test. The FDA recommends persistent pigment darkening test as the standard method of in vivo UVA testing. Persistent pigment darkening consists of UV radiation-induced skin pigmentation that persists from 2 to 24 hours after irradiation; it occurs as a result of oxidation and redistribution of pre-existing melanin; no neomelanogenesis occurs. The recommendation is to use a radiation source that emits in the range of 320 to 400 nm. In addition, visible and infrared radiation should be avoided and optical radiation from 250 to 320 nm should be less than 0.1% of the optical radiation between 320 and 400 nm. The recommended required sample size for testing is 20 to 25 individuals, with the concentration of sunscreen product to be applied at 2 mg/cm^2. UVA protection factor is defined as the ratio of the minimal pigmentation dose in sunscreen-protected skin to the minimal pigmentation dose in unprotected skin, evaluated between 3 to 24 hours after the irradiation.[19] Table IV demonstrates the grading of UVA protection factor.

In vitro test. Because UVA2 is the portion of UVA mostly represented in the persistent pigment darkening testing, the recommended in vitro FDA testing provides a measure of UVA1 protection by the calculation of the ratio of UVA1 (340-400 nm) absorbance to total UV (290-400 nm) absorbance; therefore, the in vitro method is heavily weighted toward UVA1. This method measures the quantity of UV radiation that is transmitted through roughened optical-grade quartz plates by spectophotometry before and after the application of the sunscreen product at 2 mg/cm^2. The recommended radiation source is a xenon arc solar simulator that ranges from 290 to 400 nm. Because of concerns of photostability of sunscreens, a pre-irradiation dose is incorporated based on a calculation that takes into account the SPF of the sunscreen. The in vitro rating system is outlined in Table IV.

The final UVA rating is determined by a combination of both in vivo and in vitro testing, as illustrated in Table IV. If discordances occur between in vivo and in vitro testing, the final rating will be the lowest rating determined by either in vitro or in vivo testing. Therefore, a high in vivo rating and poor in vitro

rating may be a result of considerable UVA2 absorbance; conversely, a high in vitro rating and poor in vivo rating may be a result of considerable UVA1 absorbance. Products that do not achieve a 1-star rating need to state that they have no UVA protection.

Water-resistance requirements. For sunscreen products that claim water resistance, the label SPF and appropriate UVA grading should be the values of testing determined after 2 × 20 minutes and 4 × 20 minutes of water immersion for water-resistant and very water-resistant products, respectively.

Directions for use and labeling requirements. The FDA proposes requiring the following sun alert statement as the first sentence in bold type in the "Warnings" section of all over-the-counter sunscreen products, with the exception of lip cosmetic-drug and lip-protectant products: "UV exposure from the sun increases the risk of skin cancer, premature skin aging and other skin damage. It is important to decrease UV exposure by limiting the time in the sun, wearing protective clothing, and using a sunscreen." In addition, the FDA proposes the following directions of use: to apply "liberally," "generously," and "evenly" before sun exposure; "apply and reapply as directed to avoid lowering protection"; and "reapply at least every two hours." As an option, the label may also state "apply to all skin exposed to the sun."

Products that do not satisfy the water-resistant or very water-resistant testing procedures should state "reapply at least every two hours and after towel drying, swimming or sweating/perspiring." For products that satisfy the water-resistance testing procedures, the labeling should state "reapply after '40 minutes of' or '80 minutes of' swimming or sweating/perspiring and after towel drying" for water-resistant or very water-resistant products, respectively.[19]

Timeline for implementation. There was a 90-day comments period starting from the date of the release of the amendment (August 27, 2007). Once the FDA has reviewed all comments, a final ruling will be released, and manufacturers then have 18 months to comply with the final ruling.

INSECT REPELLENT

During the past 50 years, n,n-diethyl-meta-toluamide (DEET) has been the gold standard product used as insect repellent, largely because of its efficacy and broad spectrum. DEET is available in concentrations ranging from 4% to 100%, with most commercial formulations containing 40% or less. Duration of activity is based on concentration, with formulations containing 6.65% lasting up to 2 hours and those with 23.8% lasting for 5 hours.[20] Many DEET-containing products recommend reapplication no sooner than every 6 hours.

Table IV. Grading system of the level of ultraviolet A protection proposed in the 2007 amendment to the 1999 Food and Drug Administration sunscreen monograph

Rating	Star	UVA1/UV	UVA-PF
No UVA protection	None	<0.2	<2
Low	*	0.2-0.39	2 to <4
Medium	**	0.4-0.69	4 to <8
High	***	0.7-0.95	8 to <12
Highest	****	>0.95	>12

UV, Ultraviolet; *UVA-PF*, UVA protection factor.

Furthermore, combination products containing both insect repellent and sunscreen have become increasingly popular in recent years, with approximately 20 products available in the United States. Insect repellents such as DEET, oil of citronella, and 3-(n-Butyl-N-acetyl)-aminopropionic acid (IR3535) are used in combination with sunscreen active ingredients such as oxybenzone, octinoxate, octisalate, octocrylene, and padimate O.

Although the FDA regulates sunscreens, the Environmental Protection Agency regulates insect repellents. Although these products offer the convenience of a single application, they raise concerns about potential conflicts in the directions for use, labeling requirements, efficacy, and safety.

Directions for use and labeling requirements

Although sunscreens should be applied liberally, generously, and evenly at least every 2 hours, and even more often after water exposure and towel drying, insect repellents should be applied sparingly and infrequently, if reapplied at all. For example, some DEET products require a minimum of a 6-hour interval between applications.[21]

Although more than 20 sunscreen and repellent combination products are currently available, there is still limited evidence on the efficacy and safety of such combination products, and on the application of individual products concomitantly.

Montemarano et al[22] showed an average of 33% reduction in SPF of a commercially available sunscreen containing oxybenzone, octinoxate, and octisalate when applied concurrently with DEET compared with sunscreen alone, suggesting that DEET may have thinned or disrupted the protective layer formed by the sunscreen. There was a trend for sunscreen to retain more SPF when the administration of DEET was delayed although a reduction in SPF was still present. Reduction in SPF is perhaps even more concerning when one considers that the average

person applies sunscreen in a lower concentration compared with the amount used in testing situations, effectively reducing its SPF by 50% to 75%.[23]

On the other hand, a study by Murphy et al[24] suggested the converse is likely not true. Concurrent sunscreen application did not reduce the efficacy of DEET when compared with insect repellent alone.

Safety

Safety concerns regarding insect repellents have been a long-standing issue. DEET, in particular, has raised concerns because of its odor, damaging effects on fabrics, and speculated risks of cancer and neurologic disease. Most of these associations are unfounded, and the safety record of DEET is excellent when used properly. In 50 years, there have been 43 reported cases of DEET toxicity, including 25 cases of central nervous system symptoms, one case of cardiac toxicity, and 17 allergic/cutaneous reactions. Almost all cases are a result of prolonged use or oral ingestion.[22,25] The American Academy of Pediatrics continues to endorse the use of DEET in infants and children older than 2 months, limiting application to once daily and to concentrations no greater that 30%.[26]

Designed as topical agents, repellents and sunscreens under ideal application conditions should exert minimal transdermal and systemic absorption. Animal[27,28] and human[29] studies have indicated that when individually applied, DEET is capable of transdermal and systemic absorption. Furthermore, studies with human volunteers have indicated that oxybenzone is also capable of transdermal and systemic absorption.[30,31] Furthermore, preliminary evidence suggests that concomitant administration of DEET and oxybenzone may increase absorption, and perhaps, toxicity, of both products.[32-35] A study by Ross et al[32] using a hairless mouse model demonstrated a 3.4-fold greater penetration of DEET in a sunscreen-repellent combination product containing 9.5% DEET and oxybenzone, octocrylene, and octinoxate when compared with a 20% DEET standard solution. In vitro studies using artificial membranes and piglet skin models[33,34] and in vivo[35] studies with piglet skin models found significant synergistic percutaneous absorption of both the repellent DEET and the sunscreen oxybenzone, when used in sequence as separate products, or in combinations, compared with isolated application. The percutaneous penetration profiles were dependent on the type of formulation, application sequence, and application proportion. Gu et al,[34] in 2005, suggested that such enhanced absorption may have profound effects on both the safety and efficacy of each agent and suggested that it may be reduced by application of sunscreen before the application of insect repellent rather than concurrently. In vitro experiments by Wang and Gu[29] using human skin demonstrated that human skin was less permeable to DEET and oxybenzone than artificial membranes and piglet skin, with the permeability to oxybenzone being lower than DEET. Furthermore, similar to what had been observed in previous studies, concurrent administration resulted in synergistic percutaneous absorption of both DEET and oxybenzone at varying degrees, dependent on the test formulation and application approaches. Premixing repellent spray with sunscreen lotion significantly enhanced the permeation of both DEET and oxybenzone. However, premixing repellant lotion and sunscreen lotion did not result in significantly enhanced permeation in human skin, which was contrary to what was found in studies with piglet skin and artificial membranes. In addition, sunscreens and insect repellents may enhance absorption of other compounds applied to the skin. Pont et al[36] found that different sunscreens' active ingredients with and without DEET, with the exception of octocrylene, synergistically increased the penetration of the herbicide 2,4-dichlorophenoxyacetic acid. Brand et al[37] found that titanium dioxide and zinc oxide increased the transdermal absorption of the herbicide 2, 4-dichlorophenoxyacetic acid.

Conclusion

Sunscreen developments point toward broad-spectrum UVB/UVA products and photostability. Although introduction of new sunscreen actives takes time, new products with even better efficacy and safety are becoming available worldwide and will continue to do so in the future. Many sunscreen products involve the use of nanotechnology; based on current evidence, nanoparticles produced by this technology appear to be safe. The reported estrogenic effect of some UV filters appears to have no clinical relevance in human subjects. The 2007 amendment to the FDA sunscreen monograph is a welcomed step in beginning to address the UVA protection for the US public.

Combination sunscreen and insect repellent products, despite the convenience they offer, pose difficult issues with regard to both safety and efficacy. Combination products may decrease the effect of the individual agents, and increase absorption, and with it, the risk of toxicity. Perhaps the most troubling issue is that of labeling. Although sunscreen is designed to be applied liberally and frequently (at least every 2 hours), insect repellents are to be applied with caution (no sooner than 6 hours). Application of a combination product too frequently poses the risk of insect repellent toxicity, whereas

application too infrequently invites photodamage. This was the reasoning behind Health Canada's decision to discontinue combination products until more information is available.[38] Those in the United States might be prudent to follow the same approach as our Canadian colleagues on this topic.

REFERENCES

1. Food and Drug Administration, Health and Human Services. Sunscreen drug products for over-the-counter human use; final monograph. Final rule. Fed Regist 1999;64:27666-93.
2. Kullavanijaya P, Lim HW. Photoprotection. J Am Acad Dermatol 2005;52:937-58.
3. Tuchinda C, Lim HW, Osterwalder U, Rougier A. Novel emerging sunscreen technologies. Dermatol Clin 2006;24:105-17.
4. Lim HW, Naylor M, Honigsmann H, Gilchrest BA, Cooper K, Morison W, et al. American Academy of Dermatology consensus conference on UVA protection of sunscreens: summary and recommendations; Washington (DC); February 4, 2000. J Am Acad Dermatol 2001;44:505-8.
5. Shaath NA. The encyclopedia of ultraviolet filters. Carol Stream, Illinois: Allured Publishing Corp; 2007.
6. The FDA approves new over-the-counter sunscreen. FDA Consum 2006;40:4.
7. Mitchnick MA, Fairhurst D, Pinnell SR. Microfine zinc oxide (Z-cote) as a photostable UVA/UVB sunblock agent. J Am Acad Dermatol 1999;40:85-90.
8. Boniol M, Autier P, Dore JF. Photoprotection. Lancet 2007;370: 1481-2.
9. NSTC definition of nanotechnology. Available from: URL: http://www.becon.nih.gov/nstc_def_nano.htm. Accessed January 14, 2008.
10. Moloney FJ, Collins S, Murphy GM. Sunscreens: safety, efficacy and appropriate use. Am J Clin Dermatol 2002;3:185-91.
11. Gamer AO, Leibold E, van Ravenzwaay B. The in vitro absorption of microfine zinc oxide and titanium dioxide through porcine skin. Toxicol In Vitro 2006;20:301-7.
12. Pflucker F, Wendel V, Hohenberg H, Gartner E, Will T, Pfeiffer S, et al. The human stratum corneum layer: an effective barrier against dermal uptake of different forms of topically applied micronized titanium dioxide. Skin Pharmacol Appl Skin Physiol 2001;14(Suppl):92-7.
13. Lademann J, Weigmann H, Rickmeyer C, Barthelmes H, Schaefer H, Mueller G, et al. Penetration of titanium dioxide microparticles in a sunscreen formulation into the horny layer and the follicular orifice. Skin Pharmacol Appl Skin Physiol 1999;12:247-56.
14. Australian Government DoHaA, Therapeutic Goods Administration. A review of the scientific literature on the safety of nanoparticulate titanium dioxide or zinc oxide in sunscreens. Available from: URL:http://www.tga.gov.au. Accessed March 9, 2008.
15. Schlumpf M, Cotton B, Conscience M, Haller V, Steinmann B, Lichtensteiger W. In vitro and in vivo estrogenicity of UV screens. Environ Health Perspect 2001;109:239-44.
16. Ma R, Cotton B, Lichtensteiger W, Schlumpf M. UV filters with antagonistic action at androgen receptors in the MDA-kb2 cell transcriptional-activation assay. Toxicol Sci 2003;74:43-50.
17. Nakagawa Y, Suzuki T. Metabolism of 2-hydroxy-4-methoxybenzophenone in isolated rat hepatocytes and xenoestrogenic effects of its metabolites on MCF-7 human breast cancer cells. Chem Biol Interact 2002;139:115-28.
18. Janjua NR, Mogensen B, Andersson AM, Petersen JH, Henriksen M, Skakkebaek NE, et al. Systemic absorption of the sunscreens benzophenone-3, octyl-methoxycinnamate, and 3-(4-methyl-benzylidene) camphor after whole-body topical application and reproductive hormone levels in humans. J Invest Dermatol 2004;123:57-61.
19. 21 CFR Parts 347 and 352. Sunscreen drug products for over-the-counter human use: proposed amendment of final monograph; proposed rule. Fed Regist 2007;72:49070-122.
20. Scheinfeld NS. Insect repellent: more attractive to people, less attraction for insects? Cutis 2006;77:281-2.
21. Insect repellent-sunscreen drug products for over the counter human use; request for information and comments. Fed Regist 2007;72:7941-5.
22. Montemarano AD, Gupta RK, Burge JR, Klein K. Insect repellents and the efficacy of sunscreens. Lancet 1997;349:1670-1.
23. Stenberg C, Larko O. Sunscreen application and its importance for the sun protection factor. Arch Dermatol 1985;121:1400-2.
24. Murphy ME, Montemarano AD, Debboun M, Gupta R. The effect of sunscreen on the efficacy of insect repellent: a clinical trial. J Am Acad Dermatol 2000;43:219-22.
25. Fradin MS. Insect repellents. In: Elsevier S, editor. Comprehensive dermatologic drug therapy. Indianapolis: Saunders Elsevier; 2007. pp. 785-801.
26. Flake ZA, Hinojosa JR, Brown M, Crawford P. Clinical inquiries. Is DEET safe for children? J Fam Pract 2005;54:468-9.
27. Qiu H, Jun HW, Tao J. Pharmacokinetics of insect repellent N, N-diethyl-m-toluamide in beagle dogs following intravenous and topical routes of administration. J Pharm Sci 1997;86:514-6.
28. Abdel-Rahman A, Dechkovskaia AM, Goldstein LB, Bullman SH, Khan W, El-Masry EM, et al. Neurological deficits induced by malathion, DEET, and permethrin, alone or in combination in adult rats. J Toxicol Environ Health A 2004;67:331-56.
29. Wang T, Gu X. In vitro percutaneous permeation of the repellent DEET and the sunscreen oxybenzone across human skin. J Pharm Pharm Sci 2007;10:17-25.
30. Hayden CG, Roberts MS, Benson HA. Systemic absorption of sunscreen after topical application. Lancet 1997;350:863-4.
31. Gonzalez H, Farbrot A, Larko O, Wennberg AM. Percutaneous absorption of the sunscreen benzophenone-3 after repeated whole-body applications, with and without ultraviolet irradiation. Br J Dermatol 2006;154:337-40.
32. Ross EA, Savage KA, Utley LJ, Tebbett IR. Insect repellent [correction of repellant] interactions: sunscreens enhance DEET (N,N-diethyl-m-toluamide) absorption. Drug Metab Dispos 2004; 32:783-5.
33. Gu X, Kasichayanula S, Fediuk DJ, Burczynski FJ. In-vitro permeation of the insect repellent N,N-diethyl-m-toluamide (DEET) and the sunscreen oxybenzone. J Pharm Pharmacol 2004;56:621-8.
34. Gu X, Wang T, Collins DM, Kasichayanula S, Burczynski FJ. In vitro evaluation of concurrent use of commercially available insect repellent and sunscreen preparations. Br J Dermatol 2005;152: 1263-7.
35. Kasichayanula S, House JD, Wang T, Gu X. Simultaneous analysis of insect repellent DEET, sunscreen oxybenzone and five relevant metabolites by reversed-phase HPLC with UV detection: application to an in vivo study in a piglet model. J Chromatogr B Analyt Technol Biomed Life Sci 2005;822:271-7.
36. Pont AR, Charron AR, Wilson RM, Brand RM. Effects of active sunscreen ingredient combinations on the topical penetration of the herbicide 2,4-dichlorophenoxyacetic acid. Toxicol Ind Health 2003;19:1-8.
37. Brand RM, Pike J, Wilson RM, Charron AR. Sunscreens containing physical UV blockers can increase transdermal absorption of pesticides. Toxicol Ind Health 2003;19:9-16.
38. Health Canada Pest Management Regulatory Agency Regulatory Note. Personal insect repellent and sunscreen combinations (REG2000-07), 2000. Available from: URL:http://www.pmra-arla.gc.ca/english/pdf/reg/reg2000-07-e.pdf. Accessed April, 4, 2007.