ATTACHMENT
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THE COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION

E. EDWARD KAVANAUGH
PRESIDENT

September 11, 1998

Debra L. Bowen, M.D.
Deputy Director
Office of Drug Evaluation V (HFD-105)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Re: Tentative Final Monograph for OTC Sunscreen Drug Products: Docket No. 78N-0038

Dear Dr. Bowen:

I am writing on behalf of The Cosmetic, Toiletry, and Fragrance Association (CTFA) and the Nonprescription Drug Manufacturers Association (NDMA) and our joint Sunscreen Task Force to provide additional response on several issues raised by FDA staff members at our June 3, 1998 feedback meeting on sunscreen formulation. A copy of Dr. James Johnson's presentation is attached for inclusion in the docket.

We appreciated the opportunity to have discussion with you and other members of the FDA staff on how modern sunscreens are formulated. The subject matter and the questions from members of the FDA staff present underscored the importance of frequent communication between the industry and the FDA on developing product science during this lengthy rulemaking proceeding. This letter is an effort to provide additional information in response to questions asked during the meeting.

The following discussion is organized around questions asked during the feedback meeting. Where appropriate, we have cited additional references that will provide further information on the topic.

How is Sunscreen Volume Determined for Whole Body Application?

For an average size adult the required volume of sunscreen per application to achieve a 2 mg/cm^2 density application is calculated below:

Assuming "average adult" : 5'4" (163cms), 150 lbs (68kgs), 32" waist (82cms)
Whole Body Surface Area = 1.62m^2 = 16200cm^2
Minus "bathing suit" (groin area) 15cms x 82cms= 1219cm^2 (1)

1101 17TH ST., N.W., SUITE 300 WASHINGTON, D.C. 20036-4702
202.331.1770 FAX 202.331.1969
http://www.ctfa.org

Net application area » 14981 cm^2

Application Dose = 14981cm^2 x 0.002g/cm^2 = 29gms ≈ 1 fl. oz.

The application doses depend on body size and can range from
5'0, 90lb, 30" waist -----> 0.72 fl. oz. / application
6'5" 225lb, 36" waist ----> 1.5 fl oz. / application

Sunscreen products are typically sold in packages of 4 to 8 fl. oz to accommodate multiple applications.

As global harmonization of SPF testing has progressed, the 2mg/cm^2 application amount has become the world-wide standard for SPF testing. 2mg/cm^2 is not an excessive amount of product; indeed, this application amount is required to adequately and evenly cover the test site for the SPF test. After the product is applied and rubbed in, there is no visible residue on the skin.

References

1. Based on Body Surface Area estimates from: Geigy Scientific Tables. Vol. 3., Medical Education Division, Ciba-Geigy Corp. West Caldwell, NJ. Pg. 329.

What is The Significance of The Product Film on the Skin in Sunscreen Performance?

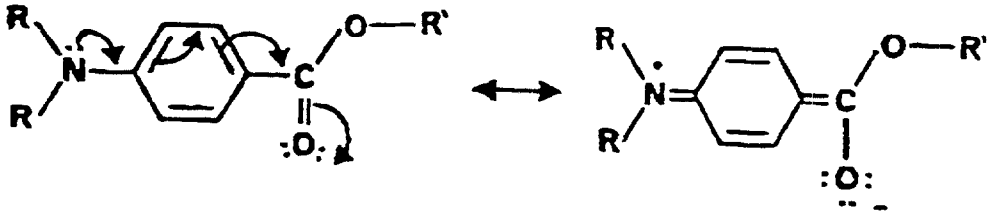
The product film on the skin is a key factor in sunscreen product performance. A sunscreen should retain its original efficacy on the skin for several hours after application. The time dependence of sunscreen efficacy has been investigated. Contrary to the suggestion that the protection provided by sunscreen products may not be maintained at the skin's surface in the product film for very long after application, published data show that sunscreen products of both high and low SPF with a variety of different vehicle types can maintain their efficacy on skin quite well[1] . Furthermore, during waterproofness testing, the product must maintain its efficacy on skin until the UV exposures are given, 2 hours or more after product application.

1. Agin PP ; Levine DJ. Sunscreens retain their efficacy on human skin for up to 8 h after application. J Photochem Photobiol B 1992, 15 (4) p371-4.

What is the Mechanism of Action of Sunscreens?

The primary means of ultraviolet radiation absorbance by Category I sunscreen actives utilized in commercial sunscreen products occurs through the mechanism of fluorescence or heat. This is true for both organic and inorganic molecules (although inorganic pigments can also reflect and scatter UV radiation)[1,2]. The degree of reflection and scattering of these pigments is strongly dependent on the particle size and shape.

This is captured in the schematic diagram below. The organic sunscreen molecules are generally aromatic compounds conjugated with carbonyl groups. They absorb the high energy ultraviolet photons, through electron resonance delocalization in the aromatic compounds, and are raised to a more energetic orbital state. The molecule quickly returns from the less stable excited state to the ground state, releasing the energy difference in longer (lower energy) wavelengths, either infrared (heat; >700nm), or visible (visible fluorescence; 400-700nm) radiation, thus satisfying energy conservation laws. At the ground state, the absorber is again available to absorb additional photons to repeat this cyclical process.[1,2] This absorption of UV and emission of visible light/heat is the basis for how sunscreens function to protect human skin from deleterious effects of UV.



In some cases, depending on the chemical structure of the sunscreen, a second pathway an excited sunscreen molecule can take involves trans-cis isomerization. This type of isomerization is well documented in the literature for octyl methoxycinnamate. Isomerization is possible due to the excited state of the molecule not retaining its rigid geometry which results in free rotation around olefinic bonds. As described previously, both isomers will release energy by emitting light or heat and return to the ground state. Continuous irradiation of these molecules with UV quickly results in a photoequilibrium between the two isomers. Fortunately, both cis and trans isomers are efficient UV absorbers.

A third route that excited state molecules can potentially take involves the molecule undergoing photochemical reaction resulting in molecular change. The category I sunscreen that exhibits this behavior to a significant level is avobenzone. This has been documented in published literature.[4] Data on the photostability of avobenzone was reviewed by the Agency in 1996. FDA permitted marketing of avobenzone in combination with specific Category I active ingredients.

Data presented by CTFA on June 3, 1998 showed that commercial products utilizing combinations of active ingredients maintain significant absorbance after irradiation with up to 50J of solar simulated UVA/UVB energy (Table II). 50J is the equivalent of 4-5 hours of summer sunlight exposure. These data demonstrate that today's formulations in the US marketplace provide dependable protection.

Photostability evaluations of single Category I ingredients in organic solvents conducted using solar simulators, in thin film conformation are reported below[4],[5,6,7]:

These data show remarkable stability characteristics at environmentally relevant UV exposure levels.

TABLE I

PHOTOSTABILITY EVALUATIONS OF CATEGORY I SUNSCREEN ACTIVES IN SOLVENTS

Absorber	% change in UV absorbance	Exposure Condition	Reference
p-Amino benzoic acid (PABA)	-3% No degradation	25 MEDs solar simulator 10 MEDs in vivo on human skin	Westerhof et al, 1986 Stenberg et al. 1987
Glyceryl PABA	-2%	25 MEDs solar simulator	Westerhof et al, 1986
Octyl dimethyl PABA	-3%; -6%	25 MEDs solar simulator	Westerhof et al, 1986; Kammayer et al, 1987
Oxybenzone	0; 0	25 MEDs solar simulator	Westerhof et al, 1986; Kammayer et al, 1987
Homosalate	-2%; -3%	25 MEDs solar simulator	Westerhof et al, 1986; Kammayer et al, 1987
2-Phenylbenzimidazole sulfonic acid	0%	25 MEDs solar simulator	Kammayer et al, 1987
Octyl methoxycinnamate	-4%	25 MEDs solar simulator, *10J/cm^2 (Deflandre & Lang)	DeFlandre & Lang, 1988
Avobenzone	-36%	1 hour sunlight	DeFlandre & Lang, 1988

Assessment of 12 different commercial sunscreen products shows only minor UV absorbance changes after significant UV exposure

TABLE II

COMMERCIAL PRODUCT PHOTOSTABILITY

Labeled SPF	Sunscreen Active System[1]	Percentage of Total UV Absorbance Remaining After UV Exposure		
		5 Joules	10 Joules	50 Joules
8	OMC, OXY	100	100	100
15	OMC, PBSA, ZnO	100	100	100
15	OMC, PBSA	100	100	100
15	OMC, OS, OXY	100	100	100
15	TiO_2, OMC	100	100	94
15	OMC, OS, TiO_2	100	97	84
15	OMC, OCTO, OXY, TiO_2	100	100	100
15	MA, OMC, TiO_2	100	99	92
15	OMC, AVO, OXY	98	94	77
30	OMC, OXY, OS	100	100	100
30	OMC, OCTO, MA, OS	100	100	100
30	OMC, OS, HS,OXY	100	100	100

Sunscreen Actives

OMC = Octyl Methoxycinnamate
PBSA = Phenylbenzimidiazole Sulfonic Acid
MA = Menthyl Anthranilate
OCTO = Octocrylene
ZnO = Zinc Oxide
OXY = Oxybenzone
OS = Octyl Salicylate
TiO_2 = Titanium Dioxide
HS = Homosalate
AVO = Avobenzone

References:
1. Lowe, N., Shaath, N. *The Chemistry of Sunscreens*, in Sunscreens: Development, Evaluation, and Regulatory Aspects. Marcel Dekker, Inc. New York. 1990. Pp. 211-233.
2. Shaath, N. *On the theory of ultraviolet absorption by sunscreen chemicals.* J. Soc. Cosm. Chem. 82: 193-207, 1987.
3. Morliere, P. et al. *A study of the photochemical behavior of sunscreens.* J. Photochem. 30:215-277, 1985.
4. DeFlandre, Lang, G. *Photostability assessment of sunscreens. Benzylidene camphor and dibenzoylmethane derivatives.* Int. J. Cosm. Sci. 10:53-62, 1988.
5. Westerhof, W., Kammeijer, J. *Suggestion for Photostable Sunscreens.* Cosmetic Dermatology. 1: 301-311, 1986.
6. Kammeyer, A. et al. *The spectral stability of several sunscreening agents on stratum corneum sheets.* Int. J. Cosm. Sci. 9:125-136. 1987.
7. Stenberg, C. et al. *Stability of PABA after UV irradiation in vivo and in vitro.* Photodermatology 4: 201-204. 1987.

Is SPF An Indicator of the Effectiveness Maintained During UV Irradiation? Does SPF Take Into Account the Photostability of the Formulation ?

Action Spectrum and SPF Testing

The action spectrum for sunburning ultraviolet radiation[1,2] extends from the UVB (290 to 320nm)into the UVA wavelengths (320 to 400 nm). UVB is more erythmogenic than UVA. A sunburn produced by solar radiation is a biological response to the UVA and UVB erythemal radiation received by the skin[3,4,5,6,7].

The contributions to efficacy from the combined active ingredients utilized in higher SPF products form the basis for the products' overall effectiveness against sunburn, which is expressed as the SPF. The SPF determined against full spectrum solar ultraviolet from either sunlight or a solar simulator measures the effectiveness of the sunscreen product against those wavelengths, i.e. 290 to 400 nm which contribute to sunburn (erythema) in one useful measurement.

To determine SPF, a clinical test is conducted which incorporates the full solar spectrum (90% UVA and 10% UVB energy) which the formulation has been designed to block. It includes exposures that exceed the SPF, utilizing multiples of the Minimal Erythemal Dose (MED), which exceed a person's natural level of protection. To deliver the labeled level of protection (for instance, 15 times the MED) a product must be able to demonstrate efficacy against sunburn throughout the full UV dose (UVA plus UVB) delivered for that SPF. The solar simulator used to test sunscreens provides a constant, but concentrated irradiance to the sunscreen on the skin during the SPF test. Inherently, this means that the formulation is effective against the solar radiation delivered to the skin to the extent necessary to provide the protection level indicated by the labeled SPF.

While the specifications for solar simulators in the Sunscreen Monograph[8] only described the required content of UVB radiation, xenon arc solar simulators filtered as described in the

monograph have always contained UVA radiation in addition to the UVB, the solar simulator used for SPF testing contains both UVA and UVB radiation. CTFA provided to FDA (3/21/94) a recommendation for revised specifications for solar simulators in comments submitted in response to the publication of the Tentative Final Monograph. A method for evaluating UVA efficacy as a separate parameter of sunscreen product performance (Critical Wavelength) was also submitted to FDA on April 9, 1996 by CTFA (RPT 9, docket 78N-0038). The Critical Wavelength procedure included a pre-irradiation step (using a solar simulator) as part of the method to ensure that photostability was accounted for in this test for broad spectrum performance.

Dose Reciprocity

Dose reciprocity is the relationship between UV intensity and time in producing a photobiological event. For most phenomena, the action is dependent on the total quantity of energy or the number of photons delivered and is independent of the dose rate or intensity.

The concept of dose reciprocity is important in sunscreen testing, whether using a solar simulator or sunlight. For erythema, dose reciprocity holds; that is, a specific number of photons can be delivered over a shorter or longer time with the same result. This is a significant concept to understand, because the performance of sunscreens under outdoor use conditions is based on results obtained using a solar simulator in the laboratory, when the rate of exposure is considerably higher than outdoors.

In addition, the UV dose used in laboratory SPF testing will vary with the Skin Type of the subject and the SPF of the product. An SPF test is a measure of the protection afforded by the sunscreen over the total irradiation dose, and mimics the actual use of the product in the real world. As the light source used simulates a summer noon spectrum, it provides the greatest total challenge to product performance, whereas in the real world, "worst case" conditions exist only during mid-day.

Sunscreen Photostability - Impact on Sunscreen Protection

Since the SPF test (performed using a high energy UVA/UVB source) simulates or exceeds a much longer sunlight exposure, the results attest to the performance of the product over the range of exposures given, which can be translated directly to extended protection time in sunlight. To produce erythema in the SPF test, some sites must exceed the protection capacity of the sunscreen so that the sunburn protection endpoint can be fully assessed. Therefore, changes in absorbance or photochemistry of the product that affect SPF erythema protection are accounted for as part of the SPF methodology; the results of the test represent a measure of any photoinstability of the product because the test assesses efficacy throughout any photochemical changes that occur during exposure.

CTFA is aware as is FDA of data in the scientific literature concerning the photostability of sunscreen formulations, including those containing the ingredient avobenzone. The studies reviewed by the Agency in support of the marketing of avobenzone in combination with other sunscreen active ingredients showed that these combinations exhibited acceptable photostability based on the results of a multiplicity of rigorous performance and safety studies. After a thorough review that included NDA data, new information and also the US marketing experience of avobenzone, the Agency concluded that "it is not aware of any safety or effectiveness problems associated with the photostability of avobenzone"[10] .

Performance studies using intense UV radiation sources

In support of the efficacy of avobenzone, data from several SPF studies were reviewed by the Agency which included efficacy testing on human subjects both before and after water exposure[9,10]. During these studies, formulations were exposed to ultraviolet radiation from a solar simulator which contained both UVA and UVB wavelengths, delivered to the test sites at an intensity of at least 10 solar constants (10 times the intensity of outdoor sunlight at noon). The formulas provided the expected protection, with no adverse experiences reported.

In addition, the UVA efficacy of avobenzone has been demonstrated using the Phototoxic Protection Factor (PPF) as well as unsensitized UVA test procedures, employing extended duration, high intensity UVA radiation delivered from xenon arc solar simulators. Again there were no adverse experiences.

The results of the studies described above (already reviewed by the Agency) show that when subjected to high intensity UVA/UVB radiation or to UVA radiation alone, sunscreen combinations with avobenzone provided the intended level of efficacy in both the UVA and the UVB wavelengths.

Conclusions

The SPF test includes exposures to UV in excess of that expected under actual use conditions. Despite the increased intensity of the ultraviolet radiation used in these test procedures in comparison to actual outdoor sunlight exposure, no performance or safety issues have been identified in clinical laboratory studies or in consumer use relative to potential negative effects of photodegradation.

While individual sunscreen ingredients may have varying photostability profiles as shown in Table I, the combination of sunscreen agents in a product formulated to provide broad spectrum protection can result in the enhancement of photostability of the formulation as evidenced by finished product efficacy (Table II).

In summary, the capacity of a sunscreen product to effectively absorb ultraviolet radiation capable of causing erythema is measured during the SPF test, which incorporates actual high energy UV exposures. Regardless of the particular sunscreen active ingredients utilized in a formulation, the overall performance maintained throughout the total UV dose given can be easily measured. Photostability of a formulation for sunburn protection is accounted for under the conditions of the SPF test.

References

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4. Sunscreen Drug Products for Over-the-Counter Human Use. Federal Register 43: No. 166, August 25, 1978:38206-38269.

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8. Sunscreen Drug Products for Over-the-Counter Human Use; Tentative Final Monograph; Proposed Rule. Fed. Reg. 58 (90), 28194-28302, 1993.

9. Sunscreen Drug Products for Over-the-Counter Human Use; Marketing Status of Products Containing Avobenzone; Enforcement Policy. Fed. Reg. 62 (83), 23350-23356, 1997.

10. Sunscreen Drug Products for Over-the-Counter Human Use: Amendment to the Tentative Final Monograph. Fed. Reg. 61 (180), 61 FR 48645, 1996.