FORMULATING SUNSCREENS WITH NEW TEA INGREDIENTS

Now that Congress has introduced a new bipartisan bicameral bill in both the Senate (S 2141) and the House (HR 4250) entitled "The Sunscreen Innovation Act," we expect to have a decision on the approval of the TEA (Time and Extent Application) soon. Already, the House has passed this bill and the Senate version is also expected to pass. The long and winding road toward the approval of eight TEA ingredients started in August of 2002—more than 12 years ago. It began with the submission to the FDA of three ingredients (amiloxate, enzacamene and octly triazone) followed by the submission in 2005 of three additional ingredients (bemotrizinol, bisoctrizol and isocotrizinol), and finally, two L'Oréal ingredients (ecamsule in 2007 and drometrizole trisiloxane in 2009) were submitted to the FDA for approval for use in the USA under the TEA guidelines (See Table I).

Belatedly, the FDA's first public action on all of those eight TEA applications came in March of this year, when the Administration announced that it found the data submitted by Symrise (for amiloxate) and 3V-Sigma (for diethyl hexyl butamidotriazone or isocotrizinol) insufficient to affirm the safety of those two sunscreen active ingredients. The agency invited the public and the manufacturers to submit additional information in support of the sunscreen actives' safety. It took 10 years to get that decision of requesting additional data—a classic example of bureaucracy at work!

TABLE 1: EUROPEAN INGREDIENTS UNDER TEA-FDA REVIEW

Ingredient	TEA Date	Docket
Amiloxate	8/14/2002	FDA-2003-N-0196
Enzacamene	8/21/2002	FDA-2003-N-0196
Octyl Triazone	8/21/2002	FDA-2003-N-0196
Bemotrizinol	4/11/2005	FDA-2005-N-0453
Bisoctrizole	4/11/2005	FDA-2005-N-0453
Isocotrizinol	9/16/2005	FDA-2006-O-0314
Ecamsule	9/18/2007	FDA-2008-N-0474
Drometrizole Trisiloxane	1/21/2009	FDA-2003-N-0196

To reiterate, what we have been complaining about for several decades is that our 17 Category I ingredients are woefully inadequate to allow for efficient and effective attenuation of harmful radiation. A simple review of those ingredients (see Table II), will quickly reveal the inadequacy of some of those filters in offering complete protection especially from UVA rays. The majority of these ingredients can be discounted. Of the 17 ingredients allowed, ecamsule (Mexoryl SX) is exclusive to L'Oréal. The following six ingredients (PABA, padimate-O, cinoxate, meradimate, sulisobenzone and trolamine salicylate) are rarely used in today's formulations for reasons discussed earlier.[2]

This leaves only 10 ingredients that could be formulated in today's US sunscreen formulations—namely octocrylene, homosalate, octinoxate, octisalate and ensulizole for UVB protection and avobenzone, oxybenzone, titanium dioxide and zinc oxide for UVA protection. Of the six UVB ingredients, ensulizole is a water-soluble filter and the remaining ingredients have some negative publicity concerning their safe use in sunscreens.

Of the four UVA ingredients, two of them, zinc oxide and titanium dioxide, cannot be used in the popular aerosol and continuous flow spray products and, due to aesthetic considerations, limit their use in emulsion formulations. Another, oxybenzone, is a weak UVA filter and has

TABLE II: FDA APPROVED LIST OF ULTRAVIOLET FILTERS (17)

Aminobenzoic acid(X)	**Octisalate**
Avobenzone (A)	**Oxybenzone (A)**
Cinoxate(X)	**Padimate O(?)**
Dioxybenzone(X)	**Phenylbenzimidazole**
Homosalate	**sulfonic acid (WS)**
Meradimate (A)	Sulisobenzone(X)
Ecamsule*[1] (A)(WS)	**Titanium dioxide (A)**
Octocrylene	Trolamine salicylate(X)(WS)
Octinoxate	**Zinc oxide (A)**
*1-Approved in L'Oreal formulations only. (A) UVA Filters (WS) Water Soluble Filters	**Bold Font: 11 active UV Filters** Normal Font: 6 rarely or never used UV Filters

Nadim Shaath
Alpha Research & Development Ltd
Email: alpharnd@aol.com

Dr. Nadim Shaath is the president of Alpha Research & Development, Ltd. in White Plains, NY. He has over 30 years of experience as chairman of the chemistry department at SUNY-Purchase and the CEO of Kato Worldwide. Recently he formed a consulting company serving the cosmetic industry called ShaathMeadows Corporation (SMC) with laboratories in New York, New Jersey, Texas, Florida and Egypt.

toxicity issues. As a result, only avobenzone offers any meaningful UVA protection. Avobenzone is notoriously photo unstable and needs photostabilizing with added quenching ingredients to survive in sunscreen formulations. Current UVB filters such as octocrylene or ecamsule are used effectively for the photostabilization of avobenzone. Other ingredients such as 2,6-diethyl hexyl naphthalate, diethyl hexyl syringylidene malonate, have been used to quench the photo-unstable avobenzone.

A recent report by Nash and Tanner[3] questioned the relevance of UV filter/sunscreen product photostability to human safety. Even though I do agree that photostability and safety are not directly correlated, photo instability leads to reduced UV filter concentration as reflected by reduced SPF. Finally, when two of the TEA ingredients, bemotrizinol and bisoctrizinol, are approved for use in the US, they can be used to impart more photostable sunscreen formulations.

The previous analysis of the currently approved filters in the US leaves little hope for improving sun care formulations in the US. One glimmer of hope will surely come from approving the pending eight TEA ingredient applications. Two of those ingredients have received notices from the FDA requesting additional safety information.[4] Of the six remaining TEA ingredients awaiting approval, two are exclusive to L'Oréal, leaving only four available for potential use in the US. Enzacamene is a camphor derivative that has received negative publicity in Europe. The three remaining filters available, one (octyltriazone-Uvinol 150 from BASF) is a UVB filter and two, bemotrizinol (Tinosorb S from BASF) and bisoctrizole (Tinosorb M from BASF), are UVA filters. It seems to me that if those ingredients are approved through the TEA process, the US will gain five very valuable ingredients in improving broad-spectrum sunscreen photoprotection in the US.

We have decided to investigate the two UVA filters that would be available worldwide when they are approved soon by the FDA; namely, bemotrizinol and bisoctrizinol. These two ingredients were originally patented by Ciba under the trade names Tinosorb S and Tinosorb M, respectively. Four years ago, BASF acquired Ciba and is currently promoting those two ingredients under the same trade names. Tinosorb S is also being sold by Ashland under the trade name of Escalol S.[5] Recently, a few Chinese suppliers (see for example MFCI under the trade name Mfsorb) have been advertising the sale of those two ingredients.[6] The user is urged to contact all suppliers of this material to inquire about patent rights and clear use of those ingredients in suncare products in the US.

With samples obtained from BASF (specifications shown on Table III and Fig.1), we created a number of bemotrizinol and bisoctrizole formulations.

We analyzed the six formulations containing bemotrizinole and bisoctrizole for stability, critical wavelength (broad spectrum protection criteria) and SPF testing (two subject in-vivo). The results are in Table IV. We have basically formulated

TABLE III: SPECIFICATIONS OF BEMOTRIZINOL AND BISOCTRIZOLE (6)

Chemical Name:	**Tinosorb S**	**Tinosorb M**
Structural Formula:		
Molecular Formula:	$C_{38}H_{49}N_3O_5$	$C_{41}H_{50}N_6O_2$
Molecular Weight:	627.8 g/mol	658.86 g/mol
INCI name:	Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine (BEMT)	Methylene Bis-Benzotriazoyl Tetramethylbutylphenol (and) Aqua (and) Decyl Glucoside (and)Propylene Glycol (and) Xanthan Gum
USAN name:	Bemotrizinol	Bisoctrizole
CAS-No:	187393-00-6	103597-45-1
Physical Appearance:	Light yellow powder	Aqueous white dispersion (50% active)
λmax:	310 nm and 340 nm	305 nm and 360 nm
E(1%,1cm):	819 (in ethanol, 340nm)	480 (in water, 360 nm)
λc (critical wavelength)	373 nm	388 nm
UVA/UVB ratio:	0.73	1
Recommended Level (%)	10% in Australia and EU. 3% in Japan	20% (10% active) in Australia, EU and Japan

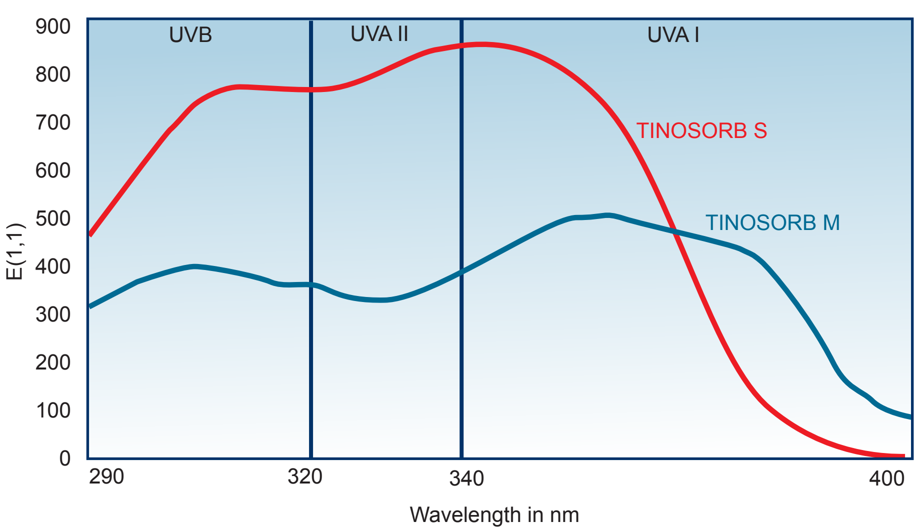

Fig 1: The UV Spectrum for bemotrizinol (Tinosorb S) and bisoctrizole (Tinosorb M)

TABLE IV: IN-VIVO/IN-VITRO TESTING RESULTS OF SUNSCREENS[8]

	SPF (2 subjects)	λc (Broad Spectrum Protection)	Comments
A	51.75	380 nm	Maximum SPF protection with Avobenzone
B	26.75	378.3 nm	Moderate SPF protection with Avobenzone
C	48.37	379 nm	Maximum SPF protection without Avobenzone
D	30.88	378 nm	Moderate SPF protection without Avobenzone
E	59.40	379 nm	Maximum SPF protection with Inorganic Particulates
F	28.75	379 nm	Moderate SPF protection with Inorganic Particulates

several nonionic oil-in-water emulsions excluding octinoxate and oxybenzone. The first set of formulations contained avobenzone photostabilized by octocrylene, bemotrizinol and bisoctrizole. Formulation A had a high SPF and B a moderate SPF. The second set were formulated without avobenzone (Formulations C and D) and the third set was formulated with the inorganic particulates, zinc oxide and titanium dioxide (Formulations E and F). The results are shown in Table IV.

1. Sunscreens with Avobenzone

We have stabilized avobenzone with only the currently approved UVB ingredient octocrylene, and the potentially TEA approved bemotrizinol and bisoctrizole. Any restrictions of use of octocrylene with avobenzone need to be observed. The two UVA TEA ingredients offer photostability to avobenzone and SPFs of 50+ designation are easily achieved. The Broad Spectrum protection, the Critical Wavelength λc was 380 nm for the maximum SPF protection (51.75) formulation A and λ c was 378.3 nm for the moderate SPF protection (28.75) formulation B.

2. Sunscreens without Avobenzone

Our formulations clearly demonstrate that with the use of the standard UVB filters and the two TEA-UVA ingredients (bemotrizinol and bisoctrizole), avobenzone is not required to achieve Broad Spectrum protection. Excellent photostability is inherent in the ingredients themselves and medium to high SPFs can be achieved. Formulation C had an SPF of 48.38 and aλc of 379nm. Formulation D had an SPF of 30.88 and a $λ_c$ of 378 nm.

3. Sunscreens with Inorganic Particulate Filters

Several formulations were made with combinations of zinc oxide and titanium dioxide augmented by the two new TEA UVA ingredients only. Extremely photostable formulations with medium to high SPF (50+) and broad spectrum protection were achieved. Formulation E yielded an SPF of 59.4 and a λ c of 379nm, and formulation F had an SPF of 28.75 and aλc of 379nm. Note that bisoctrizole has a λmax at 360nm (UVA-absorbance) with a critical wavelength λc of 388nm contributing to significant broad spectrum protection. Both ingredients are photo-stable broad spectrum UVA filters and have been used safely and effectively in Europe, Japan, Australia and elsewhere for over a decade already (see Table III).

Effective sunscreens from Europe may soon spread to the US.

In conclusion, the US sun care industry will benefit greatly from the approval of the pending TEA ingredients, especially the four UVA filters (L'Oréal's ecamsule and drometrizole trisiloxane, bemotrizinol and bisoctrizole). Once approved and utilized by US cosmetic and sunscreen manufacturers in their formulations, extremely photostable, broad spectrum high SPF formulations would be possible. This would allow us to claim that US sunscreens are not only on-par with their European, Australian and Japanese counterpart formulations but, with our enhanced ingredients and technology, we could be superior, the best and safest that the world sunscreen industry can provide.

I would like to thank the staff of AMA Laboratories (New City, NY) for its support in performing a 2-subject in-vivo SPF test and a Broad Spectrum Critical Wavelength test for all these formulations. I would also would like to thank my partner Tim Meadows for the cosmetic formulations.

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