1. Photostability

There has been a great deal written about sunscreen photostability. The sunscreen Avobenzone appears to have received the most attention, being the subject of dozens of papers and many patents.[5, 6, 7, 8, 9, 10] Also, Octinoxate has received attention, but much of the time it is stated that the UV induced changes are merely isomerization of no consequence. Most other sunscreens appear to have received even less attention in regards to their photostability. Surprisingly, our studies indicate that some US approved sunscreen ingredients in popular commercial products exhibit poor photostability resulting in marketed products that may not meet their labeled SPF or have their claimed UVA efficacy under natural sun conditions. This problem does not manifest itself with typical solar simulator spectra, thus data obtained from laboratory SPF tests or UVA tests may not be valid and result in improperly labeled products.

In reviewing literature of previous studies, there appear to be two problems characteristic of many previous studies; 1) the sunscreens were studied in their pure state in simple solutions, and/or 2) they were invariably tested with an artificial light source that does not produce the level of instability as does the sun.

TRLI has conducted studies with Xenon arc solar simulators filtered to produce the accepted COLIPA spectra for SPF testing and filtered to meet JCIA standards (typically used for UVA in vivo testing such as the Persistent Pigment Darkening, PPD, test). Neither of the spectra produce degradation as does the actual sunlight in studies conducted from February through July of 2003 in the Daytona Beach area.

The analysis of the degradation was conducted in two basic ways; 1) a thin film (2 mg/cm2) was applied to microscope slides that were then subjected to UV light. Samples were typically exposed to 1, 2, 4, 8, and 16 MEDs and then dissolved in IPA and assayed via HPLC, or 2) thin films of product (2 mg/cm2) on quartz plates were analyzed via an in vitro monochromatic analyzer (Optometric SPF 290^{TM}) and then exposed to UV light for 1, 2, 4, 8, and 16 MEDs, re-analyzing after each exposure. Estimated SPF was examined as well as UVA effectiveness, critical wavelength and/or UVA/UVB ratio. Controls were run with both procedures. In all cases where the terminology MED is used, the more correct terminology would have been Standard Erythemal Dose (SED). The SEDs were measured by a Solar Light PMA 2100^{TM} detector with a PMA 2102^{TM} outdoor SUV detector calibrated for 21 mJ/cm^2 to produce a SED per the Mckinley-Diffey Erythemal Action spectra. The time of outdoor exposure to realize an SED varies tremendously with time of year and time of day. For example in June around midday in the Daytona Beach area, as many as 5 – 6 SEDs an hour occur, whereas in midday February or in early morning June sun the number might only be 1.5 per hour.

The following products were examined:

Formula A – A wax stick type SPF 50 + formula containing Octocrylene(Oct Cryl), Oxybenzone(Oxy B), Octinoxate(OMC), Homosalate(HMS), Octisalate (OctSal), and Avobenzone(AVB).

Formula B – a commercial SPF 30, oil in water emulsion containing Avobenzone, Homosalate, Octinoxate, Oxybenzone, and Octisalate.

Formula C – a commercial SPF 30 oil in water emulsion containing Octocrylene, Octisalate, Homosalate, Octinoxate, and Zinc Oxide.

Formula D – a commercial SPF 40 oil in water emulsion containing Homosalate, Octinoxate, Octisalate, and Oxybenzone.

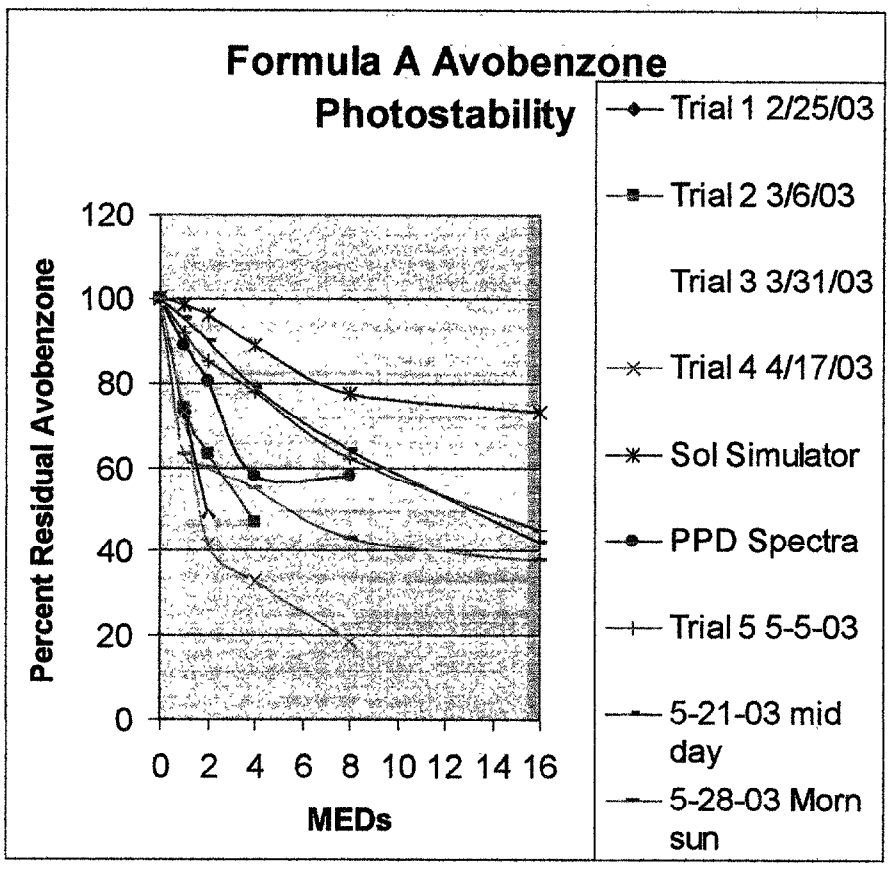
Formula E – a Canadian commercial SPF 30 oil in water emulsion containing Avobenzone, Octinoxate, Ensulizole, and Methyl Benzilidene Camphor (MBC).

Formula F – a wax stick type SPF 50+ containing Octocrylene, Oxybenzone, and Avobenzone.

Formula G – a SPF 50 water in oil emulsion containing Octocrylene, Oxybenzone, and Avobenzone.

Formula A was studied after irradiating with various spectra and differing sun times which varies the sun angle and amount of UVA per MED. The percent residual Avobenzone is shown in Figure 1.

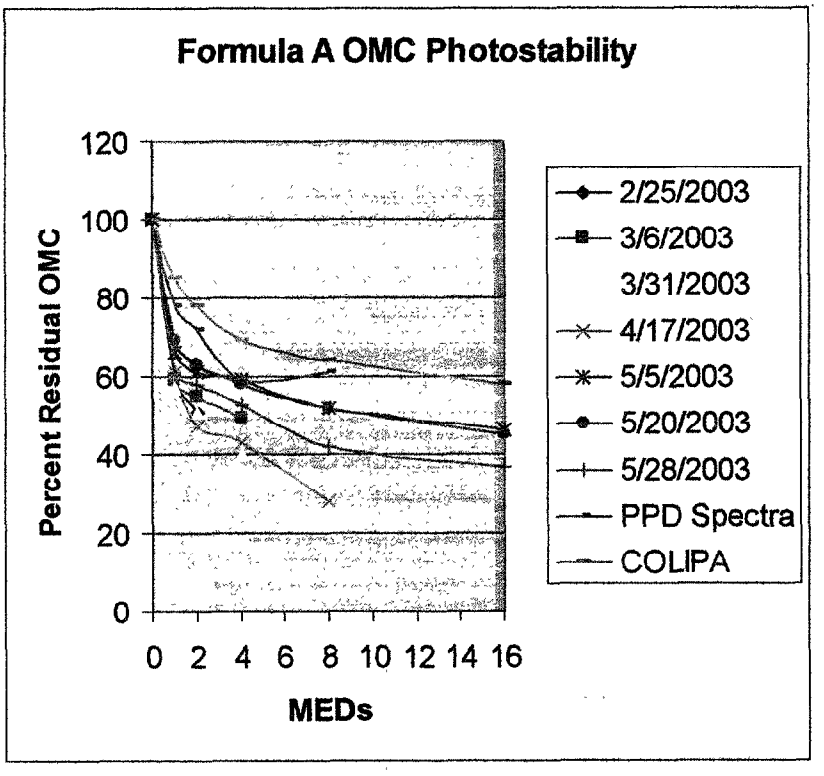
Figure 1



All curves identified by dates were based on irradiating in sunlight in the Daytona Beach Florida area. Values for the early spring data were not always available to 16 MEDs due to daily maximums available

The Formula A percentage residual OMC is shown in figure 2

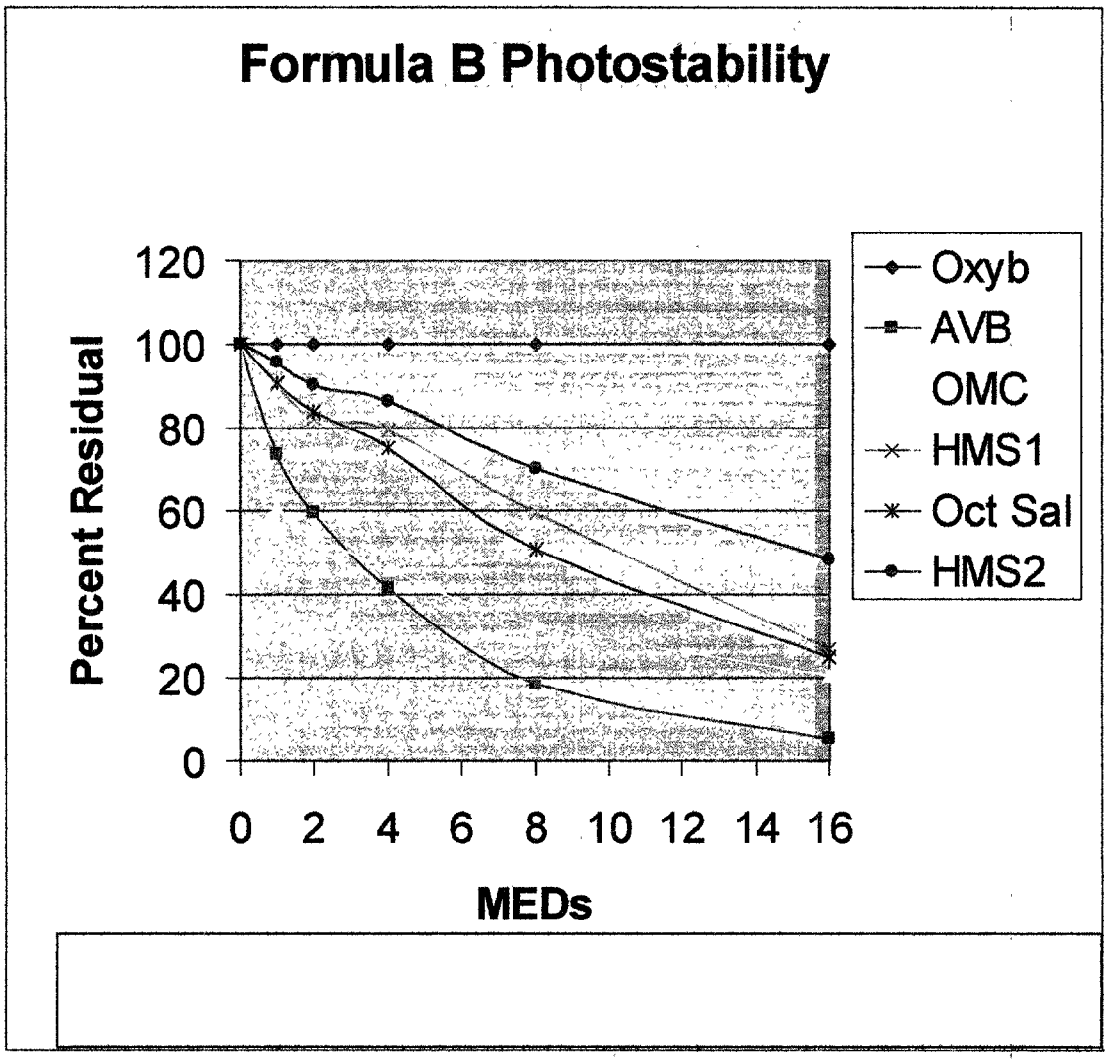
Figure 2



The 1 MED value for the COLIPA curve was extrapolated. All curves identified by dates were based on irradiating in sunlight in the Daytona Beach Florida area. Values for the early spring data were not always available to 16 MEDs due to daily maximums available. The values obtained for the 5/28/03 curves were obtained over several days, avoiding the midday sun.

Photostability tests were run on several commercial products; note Figures 3, 4, 5, and 6. All samples were irradiated in natural sunlight as indicated.

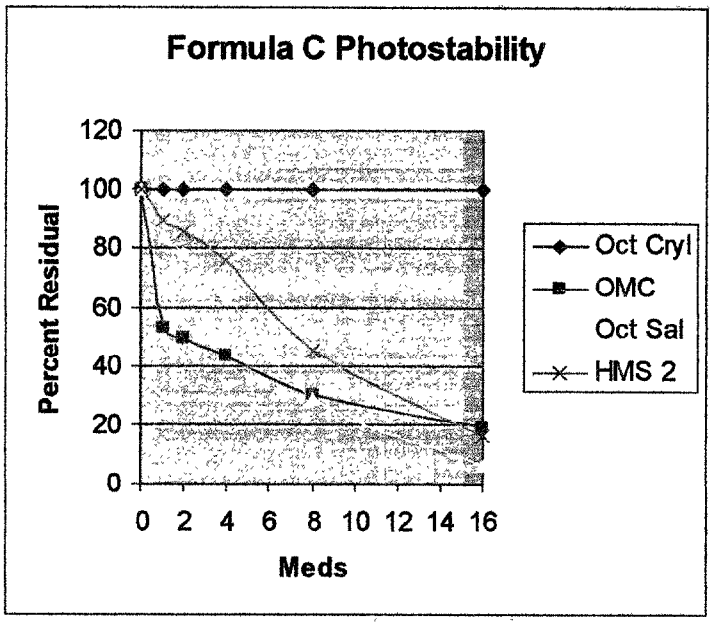
Figure 3



Formula B was irradiated in the Daytona Beach area on 5/7/03. Note that HMS 1 and HMS 2 are the two naturally occurring isomers of Homosalate that are calculated independently. Oxybenzone was used as an internal standard for the product due to the fact that in all tests it has exhibited little or no photoinstability.

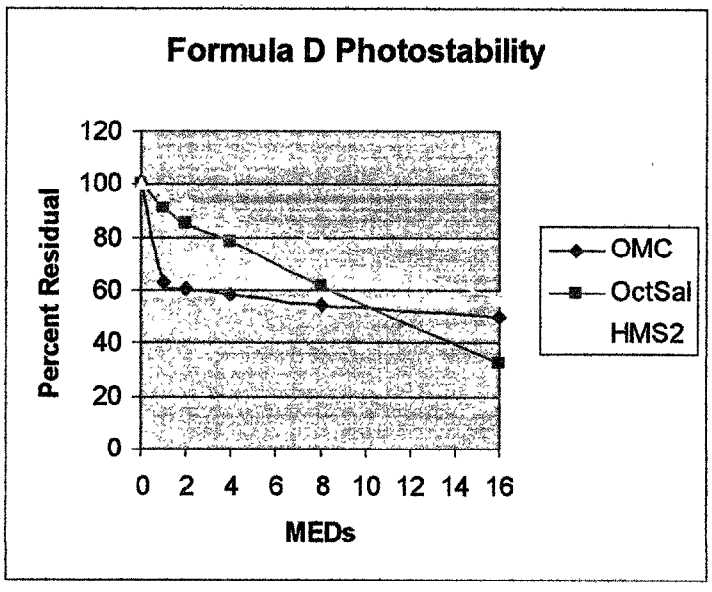
Formula B was also tested on 4/7/03(data not shown). Broken clouds and the early time of the year only yielded about 6 MEDs of UV energy. Despite this there was only about 17% OMC remaining and 0% Avobenzone remaining.

Figure 4



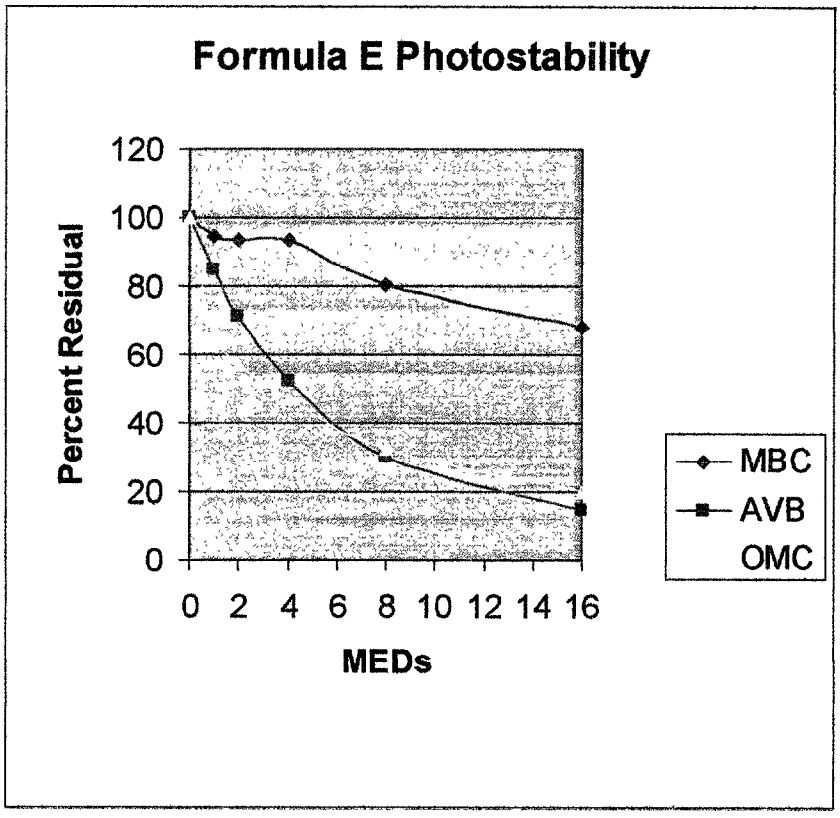
Octocrylene was used as an internal standard due to its photostability. The samples were irradiated in the sun in the Daytona Beach area on 7/17/03.

Figure 5



Oxybenzone was used as an internal standard for formula D. The samples were irradiated in the sun in the Daytona Beach area on 5/08/03.

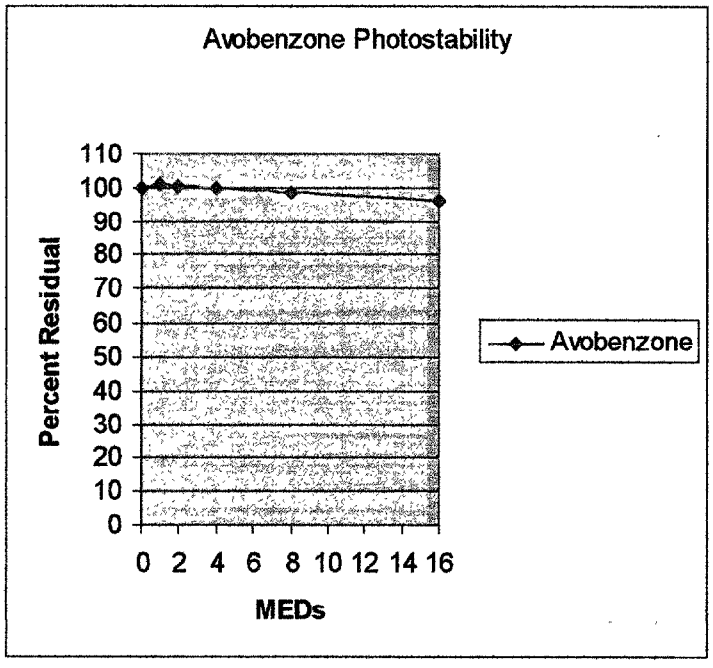
Figure 6



Formula E analysis was based on the sample weight applied to each slide. This was necessary for Formula E due to the fact that no sunscreens appeared sufficiently stable to use as an internal standard. Since no internal standard was available to accurately assess the true sample weight, the residual assayed quantity was arbitrarily and conservatively increased by 10% at each MED to account for any loss in sample preparation. The samples were irradiated in natural sun in the Daytona Beach area on 5/7/03.

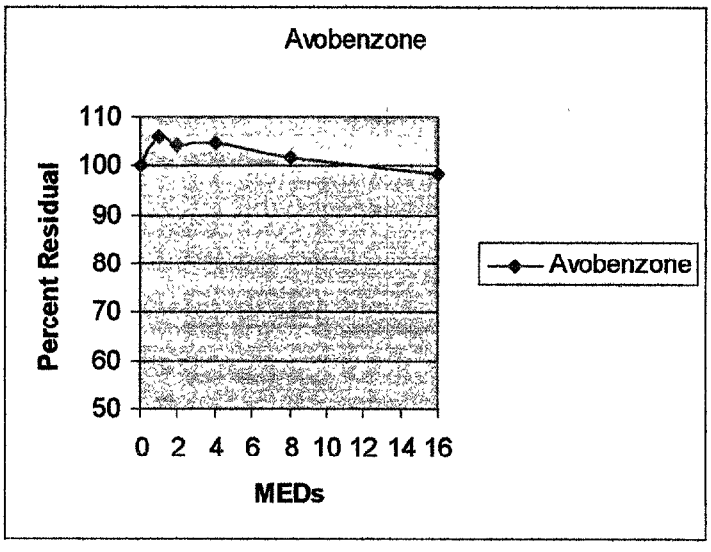
Sunscreens products do not have to be photolabile. Below are results for two TRLI experimental formulas, Formulas F and G, Figures 7 and 8 respectively.

Figure 7



Other sunscreens in Formula F exhibited equal or better stability. Oxybenzone was used as the internal standard. The samples were irradiated in Daytona Beach area sun on 6/24/03.

Figure 8



Other sunscreens in Formula G exhibited equal or better stability. Oxybenzone was used as an internal standard. The samples were irradiated in Daytona Beach area sun on 6/23/03.

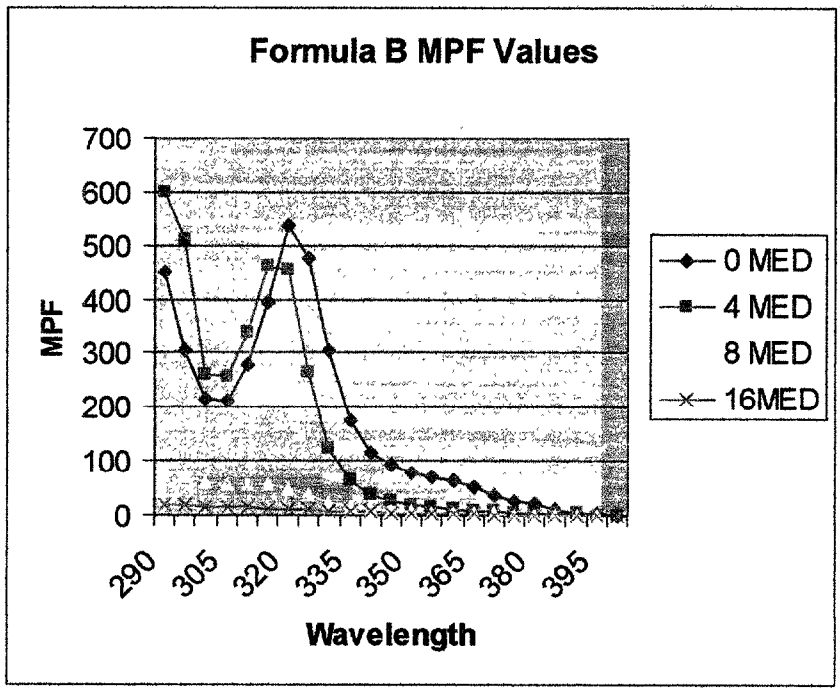
As would be predicted, products that show loss of chemical sunscreens obviously show loss of effectiveness when examined for in vitro SPF and UVA effectiveness. Table 1 is data from Formula B and was obtained by exposing in natural sunlight 2mg/cm^2 of product on quartz plates and analyzing via an Optometric SPF 290™.

Table 1(Formula B)

Meds	SPF	Critical Wavelength	UVA/B Ratio
0	120	375	0.667
1	133	371	0.521
2	106	370	0.487
4	65	365	0.432
8	21	353	0.344
16	9.6	354	0.378

Note Figure 9 showing Formula B's monochromatic protection factors (MPF) before and after irradiation.

Figure 9



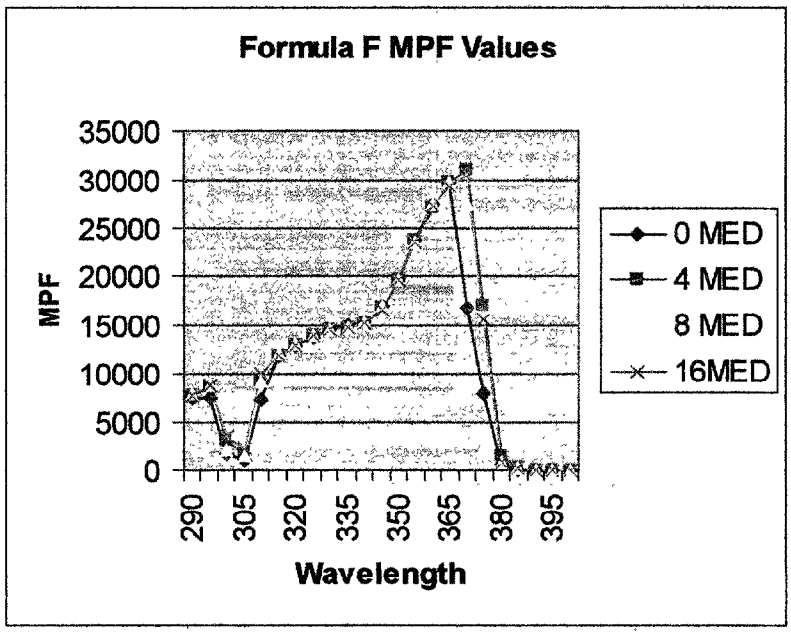
Photolability is not a given. Stable formulas can be made as can be seen from the Formula F data shown in Table 2.

Table 2(Formula F)

MED	SPF	UVA/UVB Ratio	Critical wavelength
0	290	0.913	376
1	322	0.893	376
2	307	0.904	377
4	322	0.895	376
8	310	0.912	377
16	319	0.887	376

Figure 10 show the MPF values for Formula F.

Figure 10



Both Formula B and Formula F were tested under the exact same conditions by the same technician. The irradiation was conducted on 6/10/03 and all MED time intervals were identical. Controls of each formula were kept in the dark and analyzed at the same time intervals as the irradiated samples. The controls exhibited no change. Each curve was an average of 4 scans.

It is impossible to test high SPF products in the sun, due to the length of time required to obtain the necessary MEDs. However, it was theorized that Formula B's SPF would be so low in actual sun conditions that the SPF could possibly be checked. To test this, two subjects were tested in the sun and also in the laboratory with a xenon arc solar simulator. The laboratory tests resulted in about a 25 to 30 SPF, similar to the label claim. In the sun the product was tested as if it was about a 6 to 8 SPF. One subject did not produce a response up to about a 10 SPF, indicating the SPF was higher than a 10. The other subject showed very intense positive responses at every sub site. It was impossible to tell if the response was sunburn or a PPD reaction with the naked eye but believed to be both. The response was immediate and was even darker after 24 hours. When the sub sites were measured with a chromameter they exhibited increasing red values as compared to unexposed skin, indicating the SPF was very possibly lower than a 4 on this subject. The UVA protection was also extremely low as would be predicted by the UVA/UVB ratio and critical wavelength shown in the data in Table 1.

Discussion

Figures 1 and 2 graphically indicate the significance of spectra to photostability. The residual Avobenzone and OMC vary tremendously depending on the spectra. They degrade more rapidly in the sun and more rapidly in early spring sun, presumably due to a higher ratio of UVA energy per MED. When tested in late June sun the Avobenzone degraded much more rapidly in morning sun than mid day sun per MED of exposure. This means that for any photolabile product the present laboratory SPF test and UVA tests are not an adequate indicator of efficacy in natural sunlight. In mid summer in the Daytona Beach area, 30 MEDs can be achieved in a day's time, requiring a minimum of a SPF 30 to provide all day protection. SPF 30 or higher photolabile products will not protect all day as the label would suggest.

The commercial products tested were not obscure products, but in each case mainstream, large volume products similar to many marketed products. The sunscreen combinations are very commonly used. With the exception of Formula A these products were not tested with artificial spectra. But based on data from Formula A, it is assumed the other products photostability would have fared much better in the artificial lab solar simulator spectra sources also. What is extremely clear from the studies is the fact that the products do not perform in natural sunlight as are predicted by the laboratory studies. Again noting the data in Table 1 for formula B it is seen that the predicted SPF in the sun is less than 10% of its initial value after being exposed to 16 MEDs. At the deterioration rate, the product would appear to have almost no UV absorption ability in far less than 30 MEDs of sun exposure. By reviewing all Formula B data, Figure 3, Table 1 and Figure 9 it is apparent that the product not only does not maintain the SPF, but the UVA sunscreen, Avobenzone is at a non therapeutic level after about 8 MEDs, resulting in the product having little "broad spectrum" activity.

In the last few years there has been a great debate as to whether the use of sunscreens is a risk factor for malignant melanoma.[11,12,13,14] It has been postulated that UVB

sunscreens allow users to sunbathe longer and receive higher doses of UVA energy. Also, paradoxically studies have shown that sunscreen users, especially high SPF users, sunburn more at the beach than low SPF users or non users due to longer duration in the sun.[15] High SPF, photostable products containing Avobenzone, the only US sunscreen that protects against long wavelength UVA, should alleviate both problems. Photolabile products would certainly explain why high SPF users who stay long lengths of time in the sun would tend to sunburn. Although there has not been a proven link between UVA exposure and Melanoma, UVA claims for photolabile, high SPF products would definitely not protect against that eventuality. There is a proven link between sunburn before age 18 and increased melanoma risk. Thus there is clearly a need for high SPFs and users must have photostable products that do not allow them to become sunburned.

Our work indicates a great need for a solar simulator produced spectrum that mimics the sun for photostability testing. The photostability of products appear to be dependent on the spectrum, with natural sunlight being the most detrimental. Unfortunately, it will be difficult for different labs throughout the world and even the US to standardize testing based on natural sunlight at a particular latitude and time of year. Only one paper reviewed for this writing appeared to have a spectrum that accomplished this.[7] Work needs to be conducted to determine if this spectrum produces the same relative photolability as does the sun, and a commercially available spectra source can be used to adequately mimic the sun's ability to photodegrade sunscreens. Without a standard source that mimics the sun it is difficult to define limits for sunscreen photostability, but based on our data it appears that 75% of sunscreen content can be maintained after 16 MEDs of sun exposure in all sun conditions. Perhaps this would be a reasonable limit for photostability.

There is evidence that the rates of melanoma incidences and deaths are finally ceasing to increase in the US, possibly due to the increase in high SPF sunscreen use in the past 10 – 15 years.[16] Although many sunscreen products degrade rapidly, liberal and repeated use will still offer protection, and should be a part of a sun avoidance strategy.

Photostability Conclusions

Despite the incredible amount of photostability work that has been done and reported, much more must be done. However, the upcoming monograph should insure that future product quality is the best possible and our studies do clearly lead to the following:

1) Many, if not most, US products and probably many international products are not photostable in actual sun conditions.
2) The photolability does not manifest itself in most laboratory solar simulated conditions, resulting in claimed SPF and UVA protection being overrated.
3) Some sunscreen combinations appear to be especially unstable. OMC and Avobenzone do not appear to be a stable combination. It is possible other sunscreens and perhaps some sunscreen combinations should not be approved.

4) It is possible to make photostable sunscreen combinations and formulations. This makes the laboratory SPF test and the in vitro UVA test valid predictors of protection from natural sunlight.
5) In the United States sunscreens are drug products. It is an established premise that drug products must be safe and efficacious. Sunscreen products that are not photostable satisfy neither requirement.
6) An artificial sun source that mimics natural sunlight must be developed so that photostability testing can be standardized.

2. Pass/Fail Test Method

In previous submissions to the FDA TRLI has proposed the Pass/Fail method. As further support I am attaching page proofs from a paper now approved by Photodermatology, Photoimmunology, and Photomedicine. There could be some editorial adjustments, but I would anticipate no substantial changes prior to publication. The paper clearly defines the need for a better SPF test method. The following are some of the more significant points:

1) By using the present SPF testing method, values cannot be duplicated in different laboratories.
2) The Pass/Fail SPF test is a measure of protection, not failure as is the present method. There is documented evidence that UV induced injury can occur prior to an energy dose sufficient to product erythema.
3) There is minimal UV insult to test subjects using the Pass/Fail test. The present SPF method requires erythema. The present SPF test is conducted thousands of times annually with erythema produced on several sub sites per subject, and although the test is designed to produce mild erythema, it can and must be eliminated by going to the Pass/Fail test.
4) The Pass/Fail test is a "broad spectrum" test. Reaction to UVA (tanning or PPD) also constitutes product failure. The present SPF test is a measure of erythemal injury only.

It should be noted that the FDA allows alternate test methods when validated. This method has been shown to be a more conservative *in vivo* SPF test that accounts for the significant disadvantages of the present test. There are clear and compelling reasons for the Pass/Fail SPF method to be adopted as the official method for testing sunscreen products.

3. Solar Simulator Spectra

The solar simulator spectra specification used for SPF testing is too broad! The spectra proposed by Sayre in his petition on November 7, 2001 may be realistically as tight as present technologies allow. SPFs obtained from varying spectra will vary.[1, 17] Previous submissions by TRLI have graphically shown this. However, the SPF is not as dependent on spectra if the product has "broad spectrum" absorption characteristics. If the product absorption pattern perfectly matches the erythemal action curve, then the tested SPF will not vary with different solar spectra. If the monograph requires UVA protection to the extent that the product acts as a filter across the entire erythema spectra, then the problem of different spectra giving vastly different SPF results will disappear.

4. SPF Cap

Little more can be said than what has already been said. People simply do not use enough sunscreen to obtain the tested and labeled SPF. Studies show that 25% to 50% of the laboratory tested dose is actually used by consumers. This theoretically drops the SPF to values much lower than would be expected.

One of the main objections to having SPFs higher than 30 has been the need to use excessive amounts of chemical sunscreens that might be harmful. This objection has no merit. Thousands of safety tests have been conducted with sunscreens. Topical sunscreen use is not a problem. Further to that, TRLI has shown that when stable combinations are utilized, the percent active content can be halved in most cases and still obtain the same SPF.

Therefore, the major problem with allowing unlimited SPF's is the fact that the test method cannot differentiate between small SPF increments at high SPFs. Previous submissions by me have expounded on this. The Pass/Fail method solves much of this problem since it is a conservative test requirement that the value be over the claimed (labeled) value.

5. UVA Testing and Labeling

Testing:
It cannot be overemphasized that sunscreen products must be photostable as discussed in item 1 for any UVA test, as well as SPF test, to be valid. Since the proposed UVA in vitro test is a quick scan, it will not detect photolabile products. The simulated sun spectra used for in vivo UVA testing will not degrade products as does natural sunlight. Therefore neither test is valid unless the product is photostable, and if photostable, as must be required, then the in vitro test provides a more thorough analysis not requiring further human UV exposure.

Labeling:
The most important product labeling consideration should be consumer understanding, and therefore the best possible labeling scenario would be no change. If all products of 15 SPF or higher are required to have a minimum critical wavelength and all products must satisfy photostability testing requirements, then the present SPF labeling system tells a consumer all that is needed. Any product that contains a significant quantity of Avobenzone has strong UVA protection, providing the product satisfies photostability requirements.

References

1. Uhlmann, B, Mann, T, Gers-Barlag, H, Alert, D, Sauerman, G. Consequences for sun protection factors when solar simulator spectra deviate from the spectrum of the sun. Intl. Journal of Cosmetic Science 18, 13-24(1996).
2. Hart, G, Wright, A, Cameron, R,. An Assessment of the Adequacy of Sunscreen Usage. Radiation Protection Dosimetry, Vol. 91, nos. 1-3, pp. 275-278, 2000.
3. Wulf, HC, Stender, IM, Lock-Anderson, J. Sunscreens used at the beach do not protect against erythema: a new definition of SPF is proposed. Photodermatology, Photoimmulology and Photomedicine.
4. Diffey, B. has the sun protection factor had its day? British Medical Journal, vol. 320, 15 Jan 2000.
5. Asai, M, Kawada, A, aragane, Y, Yudate, T, Isogai, R, Tezuka, T. Contact Dermatitis due to Octylmethoxycinnamate and butyl methoxydibenzoulmethane with photoaggravation. Environmental Dermatology 8: 28-30, 2001.
6. Cambon, M, Issachar, N, Castelli, D, Robert, C. An in vivo method to assess the photostability of UV filters in a sunscreen. J. Cosmetic Sci., 52, 1-11(January/February 2001).
7. Sayre, R, Dowdy, J. Photostability Testing of Avobenzone. Cos. & toiletries, vol. 114, no. 5/May 1999.
8. Schwarck, W, Rudolph, T. Photoreactions of Chemical UVA Filters in Cosmetics, GIT Laboratory Journal.
9. Chatelain, E, Gabard, B. Photostabilization of Butylmethoxydibenzylmethane(Avobenzone) and Ethylhexyl Methoxycinnamate by Bis-ethylhexyloxyphenol methoxytriazine (Tinosorb S), a new UV Broadband Filter. Photochemistry and Photobiology, 2001, 74(3): 401-406.
10. Moyal, D, Refregier, J, Chardon, A. In vivo measurement of the photostability of sunscreen products using diffuse reflectance spectroscopy. Photodermatology, Photoimmunology & Photomedicine. 2002: 18: 14-22.
11. Rigel, D. The effect of sunscreen on melanoma risk, Dermatologic Clinicss 20 (2002) 601-606.
12. Marks, R. Epidemiology of melanoma. Clinical and Experimental Dermatology, 25, 459-463.
12. Azizi, H, Iscovich, J, Pavlotsky, F, Shatir, R, Luria, I, Federenko, L, Fuchs, Z, Milman, V, Gur, E, Farbstein, H, tal, O. Use of sunscreens is linked with elevated naevi counts in Israeli school children and adolescents. Melanoma Research, 2000, 10, pp. 491-498.
13. Westerdahl, J, Olsson, H, Masback, C, Jonsson, C, Jonsson, N. Is the use of sunscreens a risk factor for malignant melanoma? Melanoma research 1995, 5. pp. 59-65.
14. Rigel, D, Naylor, M, Robinson, J. What is the Evidence for a Sunscreen and Melanoma Controversy? Arch. Dermatol./Vol 136, Dec. 2000.
15. McCarthy, E, Ethridge, K, Wagner, R. Beach Holiday Sunburn: The Sunscreen Paradox and Gender Differences. CUTIS, Vol 64, July 1999.

16. La Vecchia, C, Lucchini, F, Negri, E, Levi, F. Recent declines in worldwide mortality from cutaneous melanoma in youth and middle age. Int. J Cancer 81:62-6, 1999.
17. Sayre, R, Stanfield, J, Bush, AJ, Lott, D. Sunscreen standards tested with differently filtered solar simulators. Photodermatol, Photoimmunol, Photomed. 2001: 17: 278-283.