

## A Multi-Dimensional Approach to Improving Skin Barrier Function, Reducing Skin Sensitivity and Cosmetic Intolerance Syndrome

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### Abstract

Skin sensitivity can arise from impaired barrier function or an exaggerated response to topically applied agents which normally are minimally irritating. As we age, skin sensitivity generally increases. This is in part due to a decrease in the production of key barrier lipids, thus allowing for an increased penetration into the skin. Skin reactivity also often changes, due to the over expression or under expression of key genes involved in regulation of the inflammatory response. Together these changes are responsible for an increase in what has been recently termed "Cosmetic Intolerance Syndrome" (CIS). CIS is an idiopathic response to the use or overuse of multiple cosmetic products. CIS reactions range from simple stinging and burning to an all out allergic contact dermatitis.

We have defined a strategy to reduce CIS and increase the skin's resistance to inflammatory reactions in general. ActiLipid™ is a ceramide (glycosylated) protein mix, which in addition to improving barrier function, also up regulates the production of several ceramides. The continued use of this material will have both short term and long term effects on skin barrier function. ActiSoothe™ is a mushroom extract which down regulates COX 2 production in DNA microarray tests. COX 2 is the rate limiting enzyme in the production of prostaglandins a key mediator of the inflammatory response. In addition, ActiSoothe™ also has soothing components immediately reducing redness and irritation from sun, mechanical or chemical irritants.

Via self-assessment surveys and dermatologic referrals we recruited approximately two hundred subjects with CIS and sensitive skin. After clinical and laboratory evaluations, subjects were split into three sub groups: those with impaired barrier function (fragile skin), (1), those with hyper-reactive skin and sensitive to the application of chemical irritants (2), and those with both fragile and reactive skin (3).

TEWL loss rates and reactivity to methyl nicotinate were assessed on each subject prior to the study start and after one and two months. For one month subjects used their

normal skin care regimen, plus a fragranced facial cream, twice each day, which we felt would increase the likelihood of adverse cosmetic reactions. After this one month period subjects used the exact same regimen, however we added, 0.2% ActiLipid™, 2% ActiSoothe™, or both ingredients to the fragranced facial cream.

On the test group with increased TEWL rates ActiLipid™ reduced water loss rates and significantly reduced the number of CIS occurrences. It had only a modest affect on those subjects with hyper reactive skin. ActiSoothe™, as expected, had the opposite effect, reducing sensitivity to methyl nicotinate but having only a modest effect on subjects with elevated TEWL rates. Finally the combination of ActiSoothe™ and ActiLipid™ was extremely effective when used by subjects with both sensitive and fragile skin. The number of CIS reactions was reduced by more than 90%, reactivity to methyl nicotinate was decreased, and TEWL rates were normalized.

Sensitive skin can arise from a number of etiologies. Combining an ingredient to improve barrier function and one to reduce skin reactivity is an excellent strategy to control consumer adverse reactions and assure acceptance of cosmetic products.

### Introduction

The skin is an important interface between man and the environment. In the drier regions of the world both plants and animals have developed elaborate systems to prevent water loss. Most of these systems are based upon various lipids (fats) arranged into organized structures (membranes) to form a protective impermeable layer. This is especially true in the skin, where in the *stratum corneum* highly organized multi-lamellar structures provide protection and water impermeability.

Recently, evidence has also established that key proteins (Aquaporins) form channels into skin cells so moisture can both surround the cells and hydrate the interior. This second function is critical. While it was previously thought that cells in the outer layers of the skin were devoid of metabolic activity, we now know

this is not true and a properly hydrated cellular interior is necessary to maintain normal enzyme function and skin metabolism.

In man sphingolipids have long been recognized as an important component in the skin barrier function and have been used in a variety of moisturizing products. Ceramides, cerebrosides and sphingolipids when combined with fatty acids, cholesterol and triglycerides form stable membrane structures in the skin. These structures can be mimicked *ex vivo*, and with proper know-how skin care formulas can be developed which are similar to the skin's own membranes and can literally cure dry skin.

However sphingolipids by themselves are not very soluble and do not provide substantial immediate moisturization such as other oils or humectants do. Their unique chemical structures, while important in establishing their physiologic role, make them difficult to formulate with. Therefore the delivery system into which the sphingolipids are integrated is critical.

To overcome these inherent technical problems of sphingolipids and to maximise their bio-efficacy we have developed a lipid complex called ActiLipid™. ActiLipid™ is a ceramide (glycosylated), protein mix, which in addition to improving barrier function, also up regulates the production of several ceramides which have been shown to decrease during the ageing process. The continued use of this material will have both short term and long term effects on skin barrier function. Additionally ActiLipid™ mimics the natural membranes found in the skin, and is stable and easy to formulate with.

While barrier function is clearly import in maintaining a healthy and beautiful outer skin layer it also has a major role in controlling sensitive skin. Skin sensitivity can arise from impaired barrier function or an exaggerated response to topically applied agents which normally are minimally irritating. As we age, skin sensitivity generally increases. This is in part due to the decreased production of key barrier lipids discussed above thus allowing for an increased penetration into the skin. However, skin reactivity can also change, due to the over expression or under expression of key genes involved in regulation of the inflammatory response. Together these changes in barrier function and the skin's response to topical agents are responsible for an increase in what has been recently termed "Cosmetic Intolerance Syndrome" (CIS). CIS is an idiopathic response to the use or overuse of multiple cosmetic products. CIS reactions range from simple stinging and burning to an all out allergic contact dermatitis. Last year in this journal we described this syndrome and how the use of a topical agent ActiSoothe™ could reduce the overall end

result of CIS, i.e. adverse cosmetic reactions. ActiSoothe™ is a mushroom extract which down regulates COX 2 production in DNA microarray tests. COX 2 is the rate limiting enzyme in the production of prostaglandins a key mediator of the inflammatory response. In addition ActiSoothe™ also has soothing components immediately reducing redness and irritation from sun, mechanical or chemical irritants.

By combining ActiSoothe™ with ActiLipid™ we felt we could address both of the primary causes of CIS and sensitive skin, impaired barrier function (fragile skin) and hyper-reactive skin. The results of these tests are described herein.

## Experimental Design and Results

Via self assessment surveys and dermatologic referrals we recruited approximately two hundred subjects with CIS and sensitive skin. After clinical and laboratory evaluations, subjects were split into three sub groups: those with impaired barrier function (fragile skin), (1), those with hyper-reactive skin and sensitive to the application of chemical irritants (2), and those with both fragile and reactive skin (3).

Those in Group 1 had TEWL rates at least 50% greater than what we have observed from historical data to be normal TEWL rates (about 2.0 to 2.4 mg/cm<sup>2</sup>/sec water loss). Those in Group 2 developed erythema after application of methyl nicotinate, at very low concentrations (about one tenth of that observed typically). Finally subjects in Group 3 had both increased TEWL rates and increased sensitivity to methyl nicotinate (Table 1).

	Group 1	Group 2	Group 3
Test Parameter	Fragile Skin (Barrier Impaired)	Sensitive Reactive Skin	Fragile and Reactive Skin
TEWL (mg/cm <sup>2</sup> /hr)	3.86	2.45*	3.64
Tape Strips to 2x TEWL	2.33	3.87*	2.54
Threshold reactivity to Methyl Nicotinate (%wt/vol)	0.156	0.045*	0.056*

Table 1: Baseline Evaluations of Barrier Function and Skin Reactivity

Data is the Average of 60 Subjects  
Where indicated, \*Data is Significantly Different from Group 1,  
Student T Test  $p < 0.05$

TEWL loss rates and reactivity to methyl nicotinate were assessed on each subject after one and two month treatment regimens. For one month subjects used their normal skin care regimen, plus a fragranced facial cream, twice each day, which we felt would increase the likelihood of adverse cosmetic reactions. After this

one month treatment skin reactivity and barrier function was assessed (Table 2). No significant changes were observed, while in some cases TEWL rates directionally increased.

	Group 1	Group 2	Group 3
Test Parameter	Fragile Skin (Barrier Impaired)	Sensitive Reactive Skin	Fragile and Reactive Skin
TEWL (mg/cm <sup>2</sup> /hr)	3.95	2.61	3.72
Tape Strips to 2x TEWL	2.24	3.56	2.64
Threshold reactivity to Methyl Nicotinate (%wt/vol)	0.15	0.037	0.052

Table 2: One Month Evaluations, Treatment with Control Formulas

Data is the Average of 60 Subjects

No Significant Differences from Baseline Values (Table 1) Detected, Student T Test  $p > 0.05$

After this one month period subjects used the exact same regimen, however we added, 0.2% ActiLipid™, 2% ActiSoothe™, or both ingredients to the fragranced facial cream.

On the test group with increased TEWL rates (groups 1 and 3) ActiLipid reduced water loss rates and increased the number of tape strips to increase TEWL rates by 100%. These improvements brought these values back to normal values. It had only a modest affect on those subjects with hyper reactive skin.

	Group 1	Group 2	Group 3
Test Parameter	Fragile Skin (Barrier Impaired)	Sensitive Reactive Skin	Fragile and Reactive Skin
TEWL (mg/cm <sup>2</sup> /hr)	2.56*	2.44	2.39*
Tape Strips to 2x TEWL	3.45*	3.51	3.24*
Threshold reactivity to Methyl Nicotinate (%wt/vol)	0.171	0.073	0.087

Table 3: Two Month Evaluations, Treatment with ActiLipid™ only

Data is the Average of 20 Subjects

Where indicated, \*Data is Significantly Different from 1 Month Values (Table 2), Student T Test  $p < 0.05$

ActiSoothe™, as expected, had the opposite effect of ActiLipid™, reducing sensitivity to methyl nicotinate in groups 2 and 3, but having only a modest effect on subjects with elevated TEWL rates. As Table 4 indicates the concentration of methyl nicotinate required to induce erythema increased 3-4 fold over the values seen after one month treatment with the placebo cream.

	Group 1	Group 2	Group 3
Test Parameter	Fragile Skin (Barrier Impaired)	Sensitive Reactive Skin	Fragile and Reactive Skin
TEWL (mg/cm <sup>2</sup> /hr)	3.45	2.36	3.23
Tape Strips to 2x TEWL	2.42	3.48	2.68
Threshold reactivity to Methyl Nicotinate (%wt/vol)	0.147	0.11*	0.127*

Table 4: Two Month Evaluations, Treatment with ActiSoothe™ only

Data is the Average of 20 Subjects

Where indicated, \*Data is Significantly Different from 1 Month Values (Table 2), Student T Test  $p < 0.05$

Finally the combination of ActiSoothe™ and ActiLipid™ was extremely effective when used by subjects with both sensitive and fragile skin. The number of CIS reactions was reduced by more than 90%, reactivity to methyl nicotinate was decreased, and TEWL rates were normalized.

	Group 1	Group 2	Group 3
Test Parameter	Fragile Skin (Barrier Impaired)	Sensitive Reactive Skin	Fragile and Reactive Skin
TEWL (mg/cm <sup>2</sup> /hr)	2.71*	2.36	2.67*
Tape Strips to 2x TEWL	3.28*	3.48	3.51*
Threshold reactivity to Methyl Nicotinate (%wt/vol)	0.131	0.102*	0.132*

Table 5: Two Month Evaluations with Combined ActiSoothe™/ ActiLipid™ Formula

Data is the Average of 20 Subjects

Where indicated, \*Data is Significantly Different from 1 Month Values (Table 2), Student T Test  $p < 0.05$

## Experimental Methods

### TEWL

The measurement of trans-epidermal water loss can be very useful to test whether products are heavy and occlusive, or whether the skin of subjects is defective, and if test products can restore a normal water loss rate. Ingredients such as petrolatum, phospholipids and sphingolipids have been shown in various publications to restore abnormally high water loss rates to normal.

Barrier integrity or rates of trans-epidermal water loss is evaluated as TEWL rates in gm/m<sup>2</sup>hr, with the Evaporimeter EP1 using the 2105 probe. No modifications to the probe head are made. Normal healthy skin has in general, a TEWL of about 2-3 gm/m<sup>2</sup>hr. Prior to testing, subjects equilibrate at defined RH (between 30-40% unless otherwise defined) and temperature (68-72°C) for 30 minutes prior to testing in an isolated room. Normally test products are not applied during the morning of the test and any cleansing is completed at

least two hours prior to the test, but this can change as per protocol directions. Tested sites are all exposed to the air with no clothes covering them. After calibration of the probe as per manufacturer instructions, the probe is applied lightly to the skin surface and measurements are recorded after approximately 20-30 seconds, or until when the signal stabilizes [1]. The signal (a millivolt output) is either recorded by the technician or captured via an RS32 interface and stored on floppy disc in a data storage program. Three readings are made at each test site, if variance with any one reading is more than 40%, the measurement is discarded and repeated. The three readings are averaged and recorded as the data point.

## Methyl Nicotinate Sensitivity

Methyl nicotinate was dissolved into ethyl alcohol at increasing concentrations from 0.001% to 0.5%. The test material was applied via swab to defined areas (3x4 cm) on the volar forearm of test panelists. Application started with the lowest concentration and continued with successively higher concentrations until a visible erythema reaction was observed within 5 minutes of application.

## Barrier Disruption

Normal TEWL rates were assessed as described above. After a short equilibration period *stratum corneum* layers were removed via stripping with scotch tape. After each strip TEWL was re-measured after a short equilibration period. The process was repeated until observed TEWL rates were 100% greater than the initial rates. The number of strips required to achieve this increase were recorded.

## Conclusion

Sensitive skin can arise from a number of etiologies. Combining an ingredient to improve barrier function and one to reduce skin reactivity is an excellent strategy to control consumer adverse reactions and assure acceptance of cosmetic products. In this study, subjects who via self classification, had sensitive skin, were examined with respect to barrier function and reactivity to methyl nicotinate. We categorized test subjects into three groups, those with impaired barrier function (fragile skin), those with increased sensitivity to irritants (reactive skin), and those with both.

The three groups were treated with identical skin care products for one month test periods with either a placebo cream or the same cream with ActiLipid™ (barrier repair ingredient), or ActiSoothe™ (skin sensitivity modulator), or a combination of the two.

After one month treatment with test materials were observed the following results:

1. Treatment with ActiLipid™ reduced TEWL rates and increased the number of tape strips required to elevate TEWL rates only in the test groups where these parameters were deficient. In test Group 2, subjects only with hyper-

reactive skin, ActiLipid™ had only a modest effect on barrier function properties.

2. Treatment with ActiSoothe™ alone or in combination with ActiLipid™, increased the concentration of methyl nicotinate required to induce an erythema response by almost 10 fold in test groups 2 and 3. These groups were overly reactive to methyl nicotinate prior to treatment; however rates were within the normal range after one month treatment with 2% ActiLipid™.

The use of a barrier repair sphingolipids blend combined with an ingredient designed to reduce skin sensitivity is an excellent strategy to reduce cosmetic adverse reactions and sensitive skin of all types.

## Authors' Biographies

Dr Walter Smith is an international authority on skin care and cosmetics, with more than 30 years of research experience. After receiving a Ph. D in biochemistry in 1976, Dr. Smith spent several years at Harvard Medical School as a research professor. From 1979 to 1991 Dr. Smith worked as a research director at Richardson-Vicks, and then was with Estee Lauder as Sr. Vice President of Worldwide Research and Development. In 1991, he founded Walter Smith Consultants (WSC), to specialize in studying basic and applied aspects of skin biology. With a focus on exfoliation and skin lipids, WSC has provided a variety of clients with patented cosmetic products and technology. Dr. Smith's current research focuses health and nutrition and their impact on skin beauty, as well as the role in gene regulation in the process of skin rejuvenation. Dr. Smith is also founder of the Future Beauty Research Laboratory and Spa, an independent research laboratory dedicated to understanding the relationships between overall health, nutrition and beauty in optimizing a youthful appearance and well being. In 2002 Dr Smith joined Actifirm Inc. as Director of the Scientific and Medical Advisory Board. Dr. Smith has been granted more than 20 patents in the United States and internationally, has served on the editorial board of numerous trade journals, and has published over 60 technical papers.

Michael Bishop is a strong supporter of creating cosmetics formulated from natural, clinically effective ingredients. He has led Active Organics to be one of the largest global suppliers of naturally derived cosmetic specialty ingredients to the cosmetic industry.

After graduating from the University of California, Irvine, with a B.A. in Chemistry and a B.S. in Biological Sciences, Michael Bishop worked in exploratory development at Max Factor and later as a cosmetic development chemist for Redken Laboratories. During the late 1970's, he held the position of technical director of Life Laboratories, manufacturing pharmaceuticals and cosmetics.

Mr. Bishop has served as director of the Society of Cosmetic Chemists and is a longstanding member of the Personal Care Products Council (formerly C.T.F.A.), American Chemical Society and American Society for Quality Control.

Dr. Howard Maibach is currently Professor of Dermatology, University of California San Francisco. For more than forty years Dr. Maibach has been a leading authority in many aspects of skin biology specialising in environmental dermatology and skin toxicology. Dr. Maibach is a past president of the American Academy of Dermatology and has been a thought leader in establishing the direction and mandate of the Academy. He has been an active researcher, teacher and maintains a private practice in California.