J. Cosmet. Sci., 56, 427–444 (November/December 2005)

Ability of moisturizers to reduce dry skin and irritation and to prevent their return

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Accepted for publication May 5, 2005. Presented in part at the 58th Annual Meeting of the American Academy of Dermatology, 2000, and at the Annual Scientific Meeting of the Society of Cosmetic Chemists, December 2000

Synopsis

Assays of moisturizer efficacy have traditionally focused on a moisturizer's ability to alleviate dry skin. More recently, a moisturizer's ability to prevent primary irritation has been recognized. To assess and compare the ability of moisturizers to alleviate skin dryness and primary irritation, as well as prevent their return, four controlled-application clinical (*in vivo*) studies were carried out: hand-wash test, regression test, reduction in pre-existing irritation study, and prevention-of-irritation studies. Overall conclusions were confirmed in a home-use clinical (validation) study of people suffering from mild eczema.

The controlled *in vivo* studies demonstrate that: (a) a moisturizer can alleviate skin dryness and irritation, and prevent their return; and (b) the efficacy of different moisturizers can be differentiated, based on their composition. The home-use study results demonstrated that the most effective moisturizer identified by the controlled-application studies was highly effective against the signs of eczema.

In vivo modeling of moisturizer efficacy enables assessment and optimization of different benefits separately, while predicting the quantitative and perceived (observed) relevance of the benefits the moisturizer delivers to consumers.

INTRODUCTION

Millions of people suffer daily from skin dryness, itching, scaling, and redness due to a large variety of causes. The most common cause of skin dryness and irritation is exposure to surfactants and/or solvents, either as part of aggressive daily hygiene, repeated hand washing, exposure to cleaning solvents, or occupational activities. The skin barrier, composed of corneocytes and intercellular lipids, can only withstand a finite amount of damage until skin disease results. Predisposing factors to skin disease include low humidity conditions from cold dry weather and insufficient or defective sebum production. It is for these reasons that dry skin is more common in the winter months and

among elderly individuals. Another cause of barrier degradation is repeated wetting and drying of the skin. This occurs among individuals who lick their lips frequently or on the bottoms of children who wear diapers. Lastly, immunologic factors such as atopic dermatitis may play a role in dry skin conditions: a heightened immune response may result in asthma, hay fever, and dry skin.

Moisturizers have been traditionally used to alleviate dry skin. They can reduce transepidermal water loss by promoting barrier repair, soothe exposed dermal nerve endings by creating a temporary artificial barrier, and restore skin softness. Recently, moisturizers have been shown to prevent the induction of primary irritation and to accelerate the processes by which the skin heals itself (1–5). This is an important function, since a quality moisturizer formulation should not only reduce dry skin and irritation, but also prevent the return of these conditions, which can lead to skin disease. We demonstrate methods for modeling and quantitatively evaluating these moisturization benefits through clinical studies, followed by overall product efficacy evaluation in a home-use study.

In this paper, the four different model systems utilized will be presented in turn. For each model, the history and previous publications will be discussed first, and then the current methodology will be described. Finally, the statistical methods used to analyze the data will be shown. The results of these analyses are shown in the Results section.

MATERIALS AND METHODS: PRODUCTS TESTED

Table I shows the composition of the lotions used in this study. All were commercially available in the U.S. in 2000. It should be noted that not all products were used in each study.

MODEL SYSTEM I. BENEFIT: ALLEVIATION OF DRYNESS

MINI-REGRESSION TEST

Test history. A major cause of dry skin is the environment, especially cold winter weather

Table I
Key Ingredients Listed in Descending Order of Concentration (excluding water)

Glycerin-rich lotion (Lotion GR)	Hydrocarbon lotion (Lotion H)	Waxy lotion (Lotion W)	Butylene glycol lotion (Lotion B)	Low-glycerin lotion (Lotion LG)
Glycerin*	Petrolatum	Emulsifying wax	Butylene glycol	Glycerin
Petrolatum	Mineral oil	Glycerin	Mineral oil	Stearic acid
Cetearyl alcohol	Ceresin	Octyl isononanoate	Petrolatum	Glycol stearate
Behentrimonium chloride	Lanolin alcohol	Dimethicone	Glycerin	Sunflower seed oil
Cetyl-PG-hydroxyethyl palmitamide			Cetyl alcohol	
Oatmeal extract				
Eucalyptus extract				

* Lotion GR contains more than 15% glycerin, whereas lotions W, B, and LG contain less than 8% glycerin. Lotion H does not contain glycerin.

and the accompanying low humidity found in centrally heated homes. The regression test as developed by Kligman (6) used dry skin produced by the cold environment as a starting point for testing lotion efficacy. Panelists treated each leg with a different product (or no product), usually twice daily for three weeks. The appearance of dryness was assessed weekly. Then treatment was stopped and the time necessary for the skin to return to its original appearance was determined. Kligman reported that the composition of a moisturizer greatly affects its performance, and that a product's performance could be measured by regression testing using visual observation.

Boisits *et al.* (7) modified this procedure with daily assessments of dryness and with washing with soap to increase the drying stress on skin. This provides a constant stress on the skin to give a constant level of dryness that is observed on the "no product" control site. This is an advantage, especially in regions where weather conditions may vary during the study, resulting in changes in dryness at the control site.

Grove (2) further modified the procedure, shortening the study from up to six weeks to eight days—mini-regression testing. Participants were treated with multiple test products for four days and re-evaluated four days later. The effectiveness of moisturizers on dry skin can be evaluated using several different parameters, including visual evaluation, measuring skin hydration via conductance or capacitance, and skin color. Visual evaluation demands that a trained observer categorize the condition of a panelist's skin, using erythema and scaling grading scales. Conductance or capacitance measurements, collected using a Skicon® Dermalab or Novameter®, respectively, allow for determination of skin hydration at different times throughout a study. Colorimeter readings were used to analyze variances in skin color, in particular those associated with erythema.

Zhai and Maibach (8) and Gammal *et al.* (9) did further work using Grove's regression methodology. Zhai and Maibach reported that a single application of a moisturizer does not cause long-lasting effects, but that repeated applications of a moisturizer (that is, two times each day for seven days) can result in a significant conductance increase for at least one week after treatment has ceased. Gammal *et al.,* in evaluating the effectiveness of moisturizers on soap-induced xerosis, used clinical scaling, electrical conductance, and D-Squames® to compare products.

These previous publications contributed to the current study, which was conducted, in part, to prove that a product's ingredients contribute to its ability to provide both short- and long-term benefits.

In many of the studies discussed in this paper, relatively small panels of 25 or more volunteers were utilized. For instance, Boisits *et al.* used panels of at least 30 panelists. The panelists were selected to form a relatively homogeneous and reactive/responsive group. Previously Frosch and Kligman (10) had demonstrated that in irritation testing, such a panel predicts the reactions of a larger, general population.

Procedure. Potential panelists, after giving informed consent, were directed to use only Ivory® soap to cleanse the lower legs at home, for a minimum of three days before the start of the treatment phase, using their usual method. The subjects also were told to stop using lotions, moisturizers, oils, and soaps, other than the Ivory® soap provided, on the legs.

At the initial baseline visit, at least 25 panelists sat quietly in an environmentally controlled room (temperature at 18° to 21°C, RH = 35 ± 5%) for at least 20 minutes.

Then three test sites were designated on the lateral aspect of one lower leg of each subject, and two test sites on the other. Each site measured 5 cm by 5 cm.

To be included in the study, panelists had to show a dryness score of ≥ 2.5 on a 0-to-4 scale (see below) on all the test sites. A trained evaluator performed all dry skin evaluations in a blinded manner. Baseline (Day 0) measurements were then taken (Table II).

Measurements using a Skicon® 200 conductance meter with an MT probe were taken in triplicate at each site on each participant by a trained operator.

D-Squames® tape was then used to sample the dry flaky skin. Each test area was sub-divided into four quadrants. Each quadrant was sampled once with a D-Squames® disc during the study. Three samples were taken for determination of the desquamation index (DI) and a fourth sample for squamometry on Day 4. To sample the skin, a D-Squames® (25-mm) disc was applied to the designated site and a plunger was used to apply a constant pressure. Each D-Squames® disc was then removed and affixed to a black, labeled card. The D-Squames® discs were evaluated by computerized image analysis according to the method of Schatz *et al.* (11) to yield the desquamation index (DI).

Test lotions were assigned to the sites using a balanced complete-block design, i.e., each panelist was treated with all the test products and had a "no product" control site. The assignment of the test products to individual test sites was balanced between panelists. To each site, a technician, using a finger cot, applied 0.05 ml of the assigned test lotion (dosage = 2 mg/cm^2). A total of eight test lotion applications were made, twice daily, at least three hours apart, on Days 0, 1, 2, and 3.

Treatment was followed by a regression period of four days, during which moisturizing products could not be used on the legs. Thus, the duration of the study totaled eight days. For both the treatment period and the regression period, subjects were directed to wash their legs only with Ivory® soap. Panelists were to wash their lower legs each morning using their normal procedure similarly on each leg; otherwise the participants were to refrain from wetting their legs. On evaluation days (Days 0, 4, and 7), panelists were instructed that washing was to be at least two hours before the first visit of the day.

Each test site was re-evaluated for observer scoring, desquamation index, and conductance on Days 4 and 7. Additionally, on Day 4, a second set of D-Squames® was taken and used for squamometry readings.

Statistics. Skin hydration (conductance) and the desquamation index (DI), provided the primary measures of product efficacy. Visual evaluations and color readings of the stained D-Squames® provided secondary measures of efficacy. For skin hydration, observable

Table II
Dryness Scoring Scale

Dryness score*	Description of skin
0	No dryness
1	Slight flaking
2	Moderate flaking/scaling
3	Marked scaling/slight fissuring
4	Severe scaling/fissuring

* Half scores permitted.
A photographic scale was provided to illustrate examples of each dryness score.

dryness, and D.I., the effects of the test products were compared with each other and the "no product" control, using "change from baseline" data. Comparison with the "no product" control represented the effect of the product on the skin. By comparing the subsequent "no product" control readings to the baseline (Day 0), we can assess the effects of the environment on the skin.

For, skin hydration, DI, and observer (visual) scoring of scaling, a two-way (time × product) repeated-measure ANOVA was run using the "change from baseline" data. When an overall significant difference ($p \leq 0.05$) was detected, the products and the untreated site were compared using the Tukey HSD test.

For stained D-Squames®, statistical analyses reflected the differences between treated sites and the "no product" control site using a one-way, within-subject, ANOVA. If an overall significant difference was detected ($p \leq 0.05$), then the significance of the differences between the lotions, as well as between the untreated sites, was assessed using the Tukey HSD test.

MODEL SYSTEM II. BENEFIT: PREVENTION OF DRYNESS

HAND-WASH TEST

Test history. Repeated exposure to surfactants and water is a major cause of dry skin and eczema. Professions such as health care, hairdressing, and food preparation have elevated rates of eczema (12). Indeed, Nilsson *et al.* (13) found that nurses who wash their hands frequently have double the rate of hand eczema of a balanced cohort of clerical workers. Atopy also increased the probability of the occurrence of eczema. The hand wash methodology developed by Highley *et al.* (1) was selected as the model to assess the ability of moisturizers to prevent the induction of dryness. It is also possible to induce erythema and stratum cornuem damage, but this requires more handwashes than required to produce dryness (14).

For this study, the design of Highley *et al.* was significantly updated. Instead of small study groups ($n = 5$), larger groups of panelists ($n \geq 25$) were employed to allow for the use of better statistical methods. Furthermore, the effectiveness of multiple moisturizers was compared by trained observers, augmented with biophysical methods such as skin conductance and squamometry not available at the time of Highley's publication.

Current procedure. Thirty male and female subjects between the ages of 18 and 65 participated in this study. Panelists were in good health other than having a tendency to develop dry skin on their hands. Participants were provided with Dial® liquid soap at the beginning of the study and throughout the study. Except for using Dial® liquid soap, participants were not allowed to use any other soaps, moisturizers, creams, or lotions on the backs of their hands until the study was completed. For activities in which the backs of the hands might contact another soap or detergent, panelists were to wear the rubber gloves provided. These restrictions were imposed three days before the start of the treatment phase of the study.

At the beginning of the treatment phase, the baseline condition of the skin was determined. Panelists sat at rest in an environmentally controlled room (temperature $\leq 21°C$, RH = 35 ± 10%) for at least 15 minutes. Once acclimated, a trained observer evaluated the skin on the back of each subject's hands using a 0–4 categorical scale for skin scaling.

To qualify for the study, the backs of both hands of each participant had to have a visual scaling score of ≥ 1.5 and ≤ 2.5.

On the backs of both hands of each panelist, two 2.5-cm-diameter circles were marked. The baseline condition of each site was then evaluated using a conductance meter (Skicon® 200 with an MT probe) and a trained observer. Each subject was then given Dial® liquid soap and hand-washing instructions. At the testing laboratory, subjects washed each hand with Dial® liquid soap at intervals of approximately one hour, five times each day for four days. The hand-washing instructions required subjects to wash each hand, individually, for 60 seconds, and then both hands were rinsed for 15 seconds with warm water ($\approx$ 38° C). Following this, the backs of the hands were air-dried.

After each of the first four (4) times the hands were washed and dried, a technician applied 10 µl (or approximately 1 mg/cm^2) of test lotion to its assigned area. Assignment of three test products (lotions GR, W, and H) was based on a balanced complete-block design. The fourth site was left untreated ("no product" control). The fifth washing each day was used to eliminate residual test lotion that could hinder assessment. One hour after the fifth wash, during which panelists had re-acclimated in a controlled environment for at least 15 minutes, a clinical grader visually evaluated the hands for observable scaling, and Skicon® measurements were retaken.

In doing the evaluations, the experienced evaluator terminated any panelist from the study who received a scaling score of 4 at any of the test sites. At this time, a D-Squames® patch (used for the sampling of scaly skin) was collected for staining. The terminal measurements for each time were carried forward throughout the balance of the study.

No additional baseline evaluations were carried out after Day 0. On Day 3, after the last hand-washing and drying procedure, D-Squames® tapes were collected for staining and color evaluation (squamometry). These D-Squames® tapes were evaluated using colorimeter values (C*).

Statistics. The test lotions' ability to reduce or reverse the onset of skin dryness and dehydration (evaluated by conductance) was assessed as a "change from the baseline" scores/measurements. Comparisons of this data to that of the "no product" control site represent the effects of the test lotion on the skin. The changes from baseline for the "no product" control reflect the effect of repeated hand washing on the skin.

For daily skin hydration, as measured by Skicon® conductance, a two-way repeated-measure ANOVA was used for analysis. The significance level was set at $p \leq 0.05$. Similarly, Skicon® conductance measurements of all termination scores were analyzed using a one-way, within-subject, ANOVA. The significance level was also set at $p \leq 0.05$. For each set of measurements, if an overall significant difference was observed ($p \leq 0.05$), the test products and control site were compared using the Tukey HSD test. For observer scoring of dryness, a similar statistical approach was used.

The ability of the lotions to reduce the degree of damage to surface corneocytes was measured using stained D-Squames®. Day 3 results were compared with each other and with the untreated areas using a one-way, within-subject, ANOVA. The significance level was set at $p \leq 0.05$. When an overall significant difference was observed ($p \leq 0.05$), the Tukey HSD test was used to compare the test products and control site.

MODEL SYSTEM III. BENEFIT: PREVENTION OF PRIMARY IRRITATION

SURFACTANT PATCH TEST

Test history. Primary skin irritation can be induced by many means. These include short-term (acute) exposure to a strong irritant or repeated (chronic) exposures to a weaker, cumulative irritant. Both approaches have been used experimentally. Kligman and Wooding (15), Phillips *et al.* (16), Frosch and Kligman (10), and Simion *et al.* (17) all describe patching methods that can produce primary irritation. Justice *et al.* (18) and Paye *et al.* (19) describe an arm-immersion test that produces erythema. As the purpose of the study was to assess the ability of moisturizers to prevent primary irritation, occlusive patching with sodium lauryl sulfate (SLS) was used to induce the irritation. Pretreatment of the skin with lotion was used to assess the ability of that product to prevent irritation, when compared with skin that was not pretreated.

Similar methods have been used to assess the ability of barrier creams to reduce or even prevent the induction of irritation (20). For instance, Schentz *et al.* (21) standardized the repeated short-term occlusive irritation test (ROIT) to assess the ability of test-barrier creams to reduce irritation induced by toluene or 0.5% aqueous solutions of SLS. Sites on the volar forearm were pretreated with the test creams at 25 mg/cm^2. Ten minutes later the irritants were applied under occlusion for 30 minutes. This was repeated 3.5 hours later, and the twice-a-day treatment was used for two weeks (excluding the weekend). All four test centers found that the petrolatum-based creams were effective at reducing SLS-induced irritation as measured by TEWL rates and erythema measurements (by both trained observer and colorimeter), but appeared to have a less consistent protective effect against toluene, possibly due to the hydrophobic nature of both petrolatum and the solvent. Wigger-Alberti *et al.* (22) used a similar approach. They applied petrolatum to sites on the ventral forearms of 20 volunteers. Thirty minutes later, test irritants such as aqueous solutions of lauryl sulfate, sodium hydroxide, and lactic acid, as well as toluene, were applied for 30 minutes. This process was repeated daily for two weeks. Assessments of skin condition by erythema scoring, chromameter, and TEWL demonstrated that petrolatum could reduce irritation, although it appeared least effective against lactic acid.

Procedure. Panelists whose skin was easily irritated by surfactants were recruited for this study. After they gave informed consent, three test sites, each 2 × 3 cm, were marked on each volar forearm. The test sites were evaluated for erythema, using a 0-to-4 scale (see below), and then two test products (lotions GR and H) were applied to their designated sites, the order being reversed on contralateral arms. The middle test site on each arm was a "no product" control. Each product was applied at a dosage of 2 mg/cm^2. After the test products had dried for at least 30 minutes, a 0.5% aqueous SLS solution was applied to each test site, using an occlusive 25-mm Hill Top® chamber system (Table III).

After 24 hours, the Hill Top® chambers were removed and the test sites were rinsed with warm tap water and patted dry. A trained observer assessed erythema at each test site 24 hours after the patches were removed, using the same scale as shown above.

Statistics. The erythema responses for two sites for each product were averaged and then compared to the responses for the other product and the untreated site using a paired *t*-test, with the *p* value set at 0.013 to compensate for multiple comparisons (Bonferroni).

Table III
Erythema Scoring Scale

Erythema score*	Description of skin
0	None
1	Minimal, non-uniform
2	Moderate, uniform
3	Severe
4	Fiery red

* Half scores permitted.

MODEL SYSTEM IV. BENEFIT: REDUCTION IN PRE-EXISTING PRIMARY IRRITATION

5% IVORY® SOAP STUDY

Test history. Loden and Anderson (3) investigated whether lipids used in moisturizers affect the skin's recovery after irritation with SLS. In their study, Loden and Andersson topically applied a variety of lipids to the SLS-irritated skin of subjects. Using 1% hydrocortisone as the effective control, some lipids such as phytosterols were able to alleviate erythema. Our study protocol incorporated a modification of their methodology, substituting 5% Ivory® soap for 0.5% SLS to give a less intense, more consistent erythema reaction.

Panelists whose skin was easily irritated by surfactants were recruited for this study. Trained observers, using a 0-to-4 scale (shown above), rated the skin after it had been acclimated for at least 30 minutes (<71°F, RH = 35 ± 10%). To be included in the study, panelists had to be erythema-free (erythema score = 0) at each of eight test sites (four per volar forearm).

Twenty-five qualified panelists participated in the study. Each of eight test sites was patched with 5% Ivory® soap solution using an occlusive, 25-mm Hill Top® system. Patches remained in place for 22 hours. After the patches were removed, the test sites were rinsed with warm tap water, and then patted dry. Ninety minutes later, the panelists returned to the test laboratory, where they re-acclimated for at least 30 minutes under the environmental conditions described above, before their skin was re-evaluated for erythema.

Test sites that showed sufficient irritation (erythema $\geq$1.0 on a 0-to-4 scale) were then treated with an application of 100 ul of test material. The test sites were protected by non-occlusive 25-mm Hill Top® chambers, each of which had a ¼-inch hole punched in the top, and from which the webril patches had been removed.

After 22 hours, the protective chambers were removed and the test sites were rinsed and patted dry. Ninety minutes later, the panelists returned to the test laboratory, where they re-acclimated for at least 30 minutes under the environmental conditions described above. Finally, the test sites were re-evaluated for erythema by a trained observer.

Statistics. Erythema reduction was determined from the difference in erythema before and after the test moisturizer was applied to the irritated skin (i.e., erythema score on Day 2 minus that on Day 3). Study validation required a significantly greater reduction in erythema by 1% hydrocortisone (maximum level permitted by the FDA's over-the-

counter regulations) compared with water. Significance was determined using a paired *t*-test. The ability of the test products to reduce erythema was compared using a one-way, within-subject, ANOVA. If an overall difference were detected ($p \leq 0.05$), then the individual means were compared using a Tukey HSD test.

VALIDATION

HOME-USE STUDY

Study history. Ultimately, the clinical models are only useful if they predict the effects observed in real life. Therefore, we needed to assess whether the prediction that the high-glycerin lotion (GR) was more effective at reducing skin dryness and erythema than a lotion with much lower levels of glycerin is observed in a home-use situation. Hannuksela and Kinnunen's investigation (4) of whether moisturizers could prevent irritant contact dermatitis (ICD) caused by a detergent was used as a basis for our home-use study. Also, Zhai *et al.*'s studies (5,8), which reported on the use of dimethicone-containing skin lotions to reduce SLS-induced irritant contact dermatitis (ICD) were again utilized in this study's design.

Procedure. Sixty volunteers, both male and female, ranging in age from 18 to 90 years, participated in a two-week, double-blind, between-groups, home-use study. They were in good general health and had no skin diseases other than mild eczema on the target site, and experienced itching with minimal cutaneous findings. Panelists were not pregnant, breast feeding, or undergoing treatment for any skin condition on the body; did not have a history of allergic responses to sun exposure; did not have a history of photosensitive skin conditions; were not allergic to any ingredient in the products; and were not taking systemic analgesic or antihistamine prescriptions. They had to be willing (a) to refrain from using unapproved topical nonprescription products and prescription products on the body, and to use only the study products; (b) to sign an informed consent statement and photography release form; (c) to go to the research facility on assigned days at assigned times until the study was completed; and (d) to refrain, throughout the study, from intentional sun exposure and the use of sun lamps and tanning beds, and the use self-tanning creams and other substances designed to artificially pigment the skin. They could not concurrently participate in another research study.

Participants were equally split into two groups. One group used lotion GR and its associated mild liquid body and facial cleansers, while the other group used lotion LG, which has a substantially lower level of glycerin, and the leading U.S. liquid body and facial cleansers. All panelists were given one of two over-the-counter (OTC) analgesics for equal use on contralateral sites, as needed.

At the onset and at the end of the study, photographs were taken of the target sites on ten subjects. Subjects did not apply lotions or creams for 12 hours before the first application of the study products. Additionally, except for the face and hands, the body was not washed, and no therapeutic or ancillary products were used for two hours before the first application of the study products.

Upon their arrival at the test laboratory, panelists completed an informed consent form, and then acclimated their skin (<21°C at 30±5% RH) in an environmentally controlled room

for at least 15 minutes. The dermatologist/investigator then evaluated the subjects using a 0-to-6 scale for scaling, crusting, erythema, lichenification, roughness, and excoriation.

Subjects completed a self-evaluation questionnaire at initial baseline measurement, and then again between 15 and 30 minutes after the first product application, and at six hours, one day, one week, and two weeks. They evaluated the contralateral sites for skin softness, smoothness, moisturization, itching, dryness (look and feel), roughness, and irritation.

Skicon® 200 conductance meter (with an MT probe) and trans-epidermal water loss (TEWL) measurements were taken from the contralateral target sites at baseline, one day, one week, and two weeks.

Statistics. Biophysical measurements were analyzed using parametric statistics. The dermatologist-scored measurements and the panelists' self-assessments were analyzed using non-parametric statistics.

When the effects of using a product regimen were assessed, comparisons were made with initial baseline measurements using a Wilcoxon matched-pair rank-sum test for dermatologist assessments and self-assessments. Significance was set at $p \leq 0.05$. The paired t-test was used for biophysical measures. Comparable between-groups statistics were used to compare the effects of treatment regimens GR and LG during the study.

RESULTS

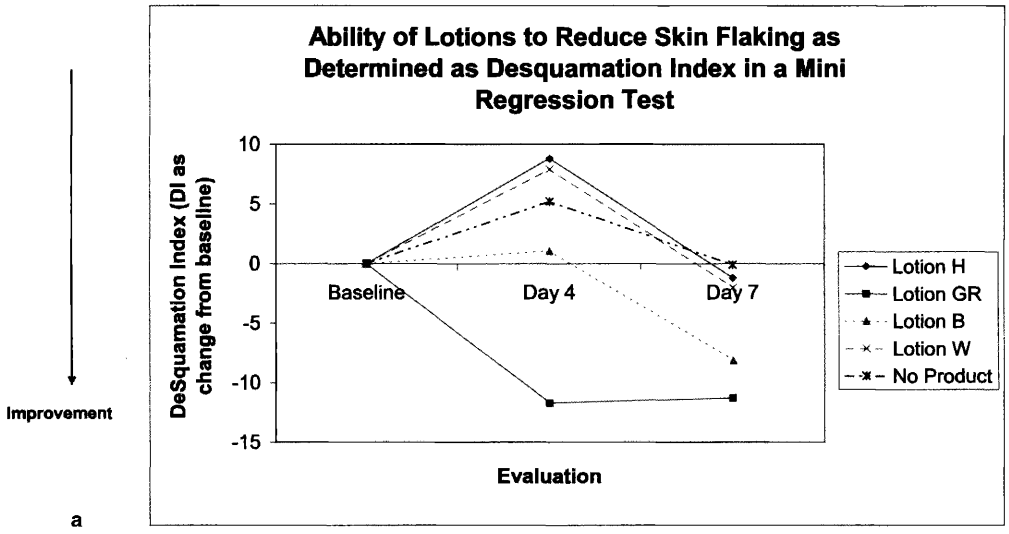
BENEFIT: ALLEVIATION OF DRYNESS—MINI-REGRESSION TEST

Four skin lotions were evaluated to discern their effectiveness at alleviating the signs of skin dryness and to determine their capacity to preclude its return. Skin hydration (conductance) and desquamation index (DI) measurements provided primary measures of efficacy. Visual evaluations of scaling and assessment of skin-surface corneocyte integrity (color readings of stained D-Squames® patches) provided secondary measures of efficacy.

Through the DI evaluation of skin flaking, a primary measure of efficacy, it was found that test product GR was significantly more effective than the other products (B, W, and H) and the untreated control in reducing skin dryness on Day 4 and in preventing its return by Day 7 (Figure 1a). Lotion B was more effective than the untreated control and lotions H and W at reducing skin flaking. The effects of Lotions H and W could not be differentiated from the "no product" control.

Measurements of skin hydration using the Skicon® 200 conductance meter showed that test products GR, W, and B significantly increased skin hydration compared to the "no product" control, whereas lotion H was not effective by this parameter. Between-treatment analysis showed that lotion GR significantly improved skin hydration compared with the other test products (B, W, and H) and the untreated control site on Days 4 and 7 ($p < 0.001$) (Figure 1b).

Analysis of the stained D-Squames® patches, a secondary measure of efficacy, showed that there was an overall significant difference ($p=0.0001$). Subsequent analysis showed that lotion GR was significantly more effective at removing damaged surface corneocytes than the other products or no treatment at all (Figure 1c).



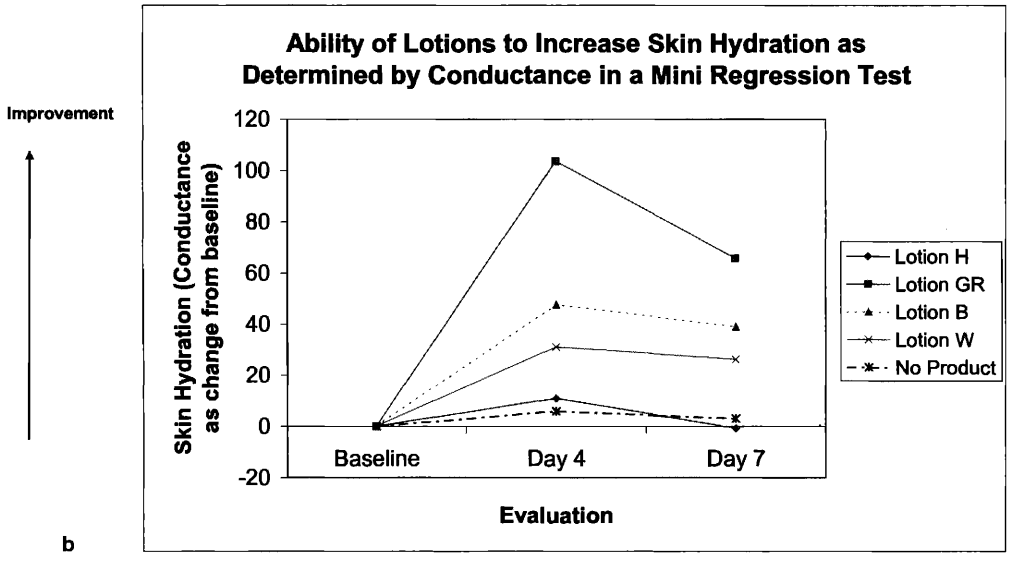
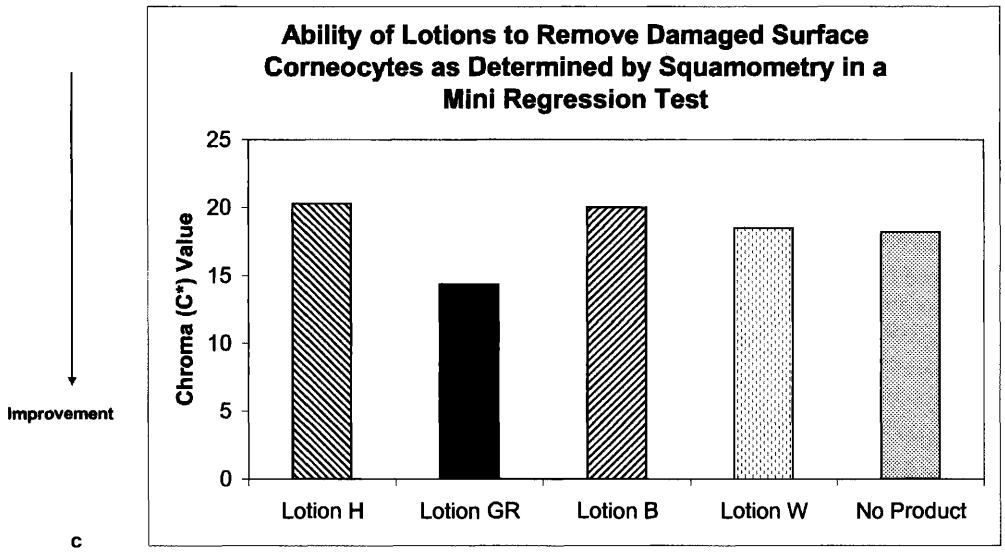


Figure 1. Alleviation of skin dryness. The ability of lotions to moisturize the skin as measured by a mini-regression test. The skin parameters assessed were: (a) Desquamation index as a measure of skin scaling. (b) Conductance as a measure of skin hydration. (c) Squamometry as a measure of surface corneocyte integrity. (d) Dryness assessed by a trained observer. (Figure continued on following page.)

Figure 1d shows the dryness scores as assessed by a trained observer. Here treatment with lotion GR significantly reduced observable scaling (when compared to the "no product" site) on Day 4. This benefit was maintained on Day 7 after treatment ceased.

BENEFIT: PREVENTION OF DRYNESS—HAND-WASH TEST

At all time measurements, product GR showed a significantly greater ability to hydrate



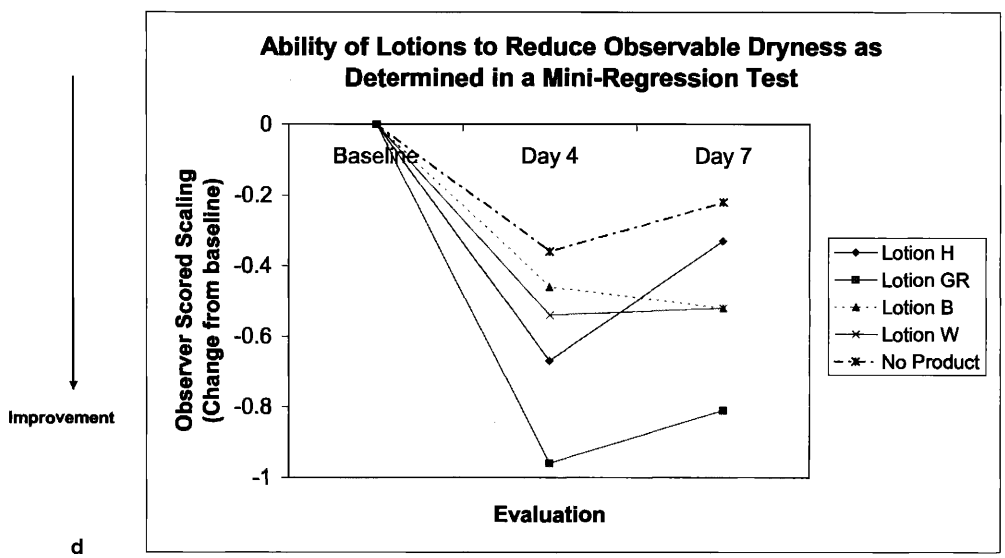
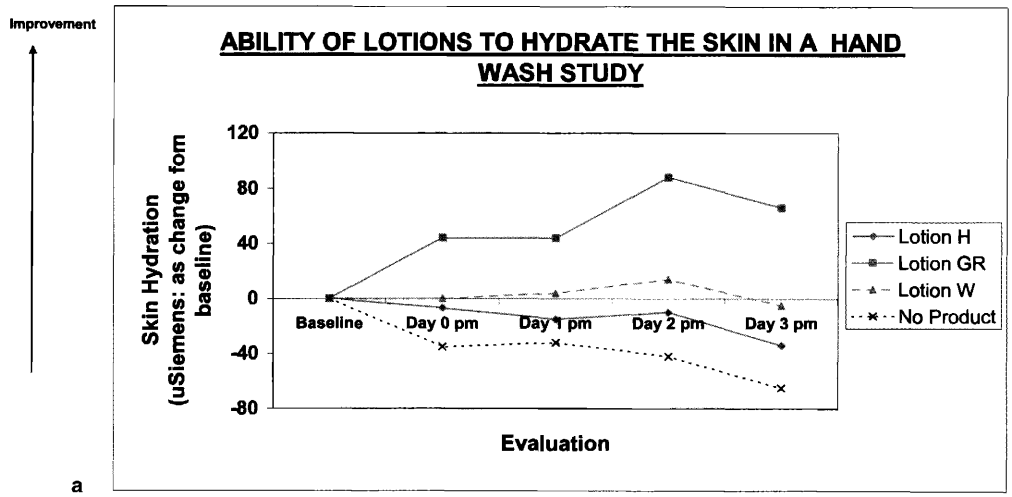


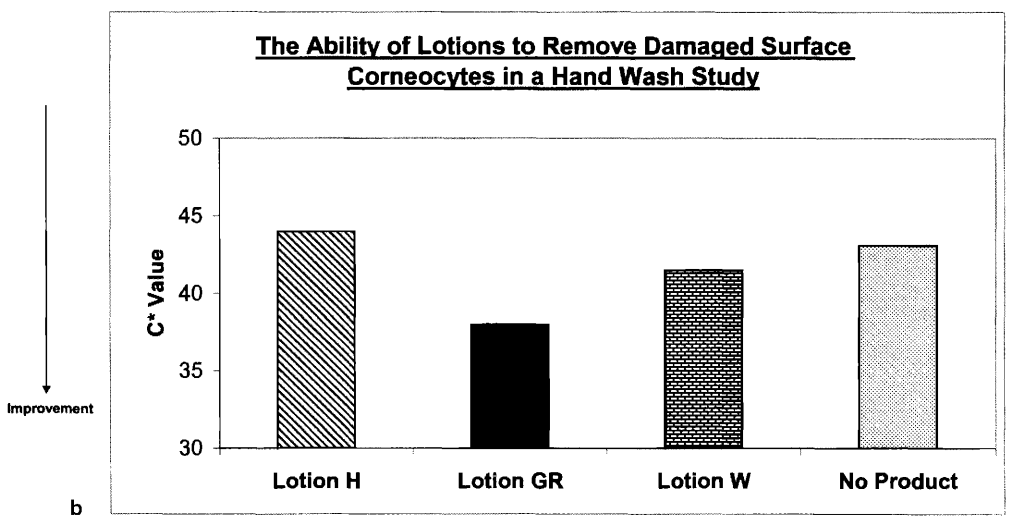
Figure 1. (continued)

the skin than the other study products (W and H) and the "no product" control, using conductance as a measure ($p < 0.01$) (Figure 2a). Application of product W had a benefit, as conductance was higher than with the "no product" control.

On Day 3, D-Squames® patches were collected from all test areas. They were subsequently stained and measured, using colorimeter C* values. Product GR was effective at removing damaged surface corneocytes, having a significantly lower C* value than the "no product" control and product H (Figure 2b).

For observer-scored scaling, a within-subject ANOVA showed that all the products were effective, with a significant reduction in scaling compared with the "no product" control





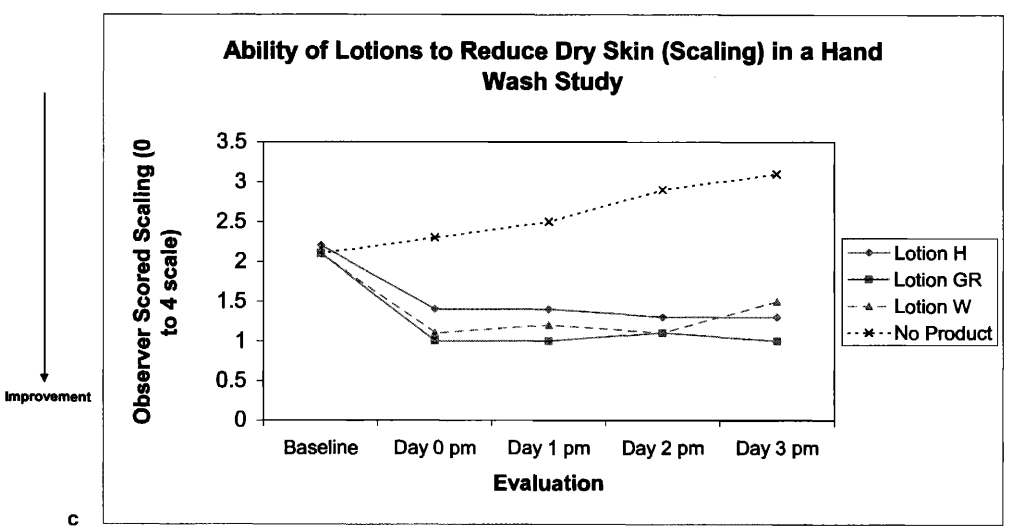


Figure 2. Prevention of skin dryness. The ability of lotions to prevent soap-inducing dryness on the backs of the hands. The skin parameters assessed were: (a) Conductance as a measure of skin hydration. (b) Squamometry as a measure of surface corneocyte integrity. (c) Dryness assessed by a trained observer.

(Figure 2c). No significant difference between products was detected. In general, it can be concluded from the conductance and the squamometry results that product GR is the most effective moisturizer at reducing or even preventing the drying effects of soap on the skin.

BENEFIT: PREVENTION OF PRIMARY IRRITATION—SURFACTANT PATCH TEST

Occlusive patching with a 0.5% SLS solution produced a moderate-to-severe level of erythema on the control ("no product") site. For the two sites exposed to the product, the data was averaged. Applying lotion H prior to the SLS solution did little to prevent the induction of erythema in comparison to the "no product" control, whereas lotion GR was able to significantly reduce erythema induction (Figure 3).

BENEFIT: REDUCTION IN PRE-EXISTING PRIMARY IRRITATION

The two controls used for this procedure were a 1% hydrocortisone gel and de-ionized water. Hydrocortisone is known to have anti-irritant properties and to significantly reduce observable, soap-induced erythema compared with water. This was found to be the case (Figure 4), and was used to validate the procedure. Lotion GR was shown to be as effective as 1% hydrocortisone at reducing erythema after 24 hours, and significantly more effective than water, the "no product" control. In contrast, 20% benzocaine, a topical analgesic that has an anesthetic mode of action, did not reduce erythema more than water.

VALIDATION: HOME-USE STUDY

Tolerability (physician–assessed). All products were well tolerated by all participants, i.e., no panelist dropped out of this study.

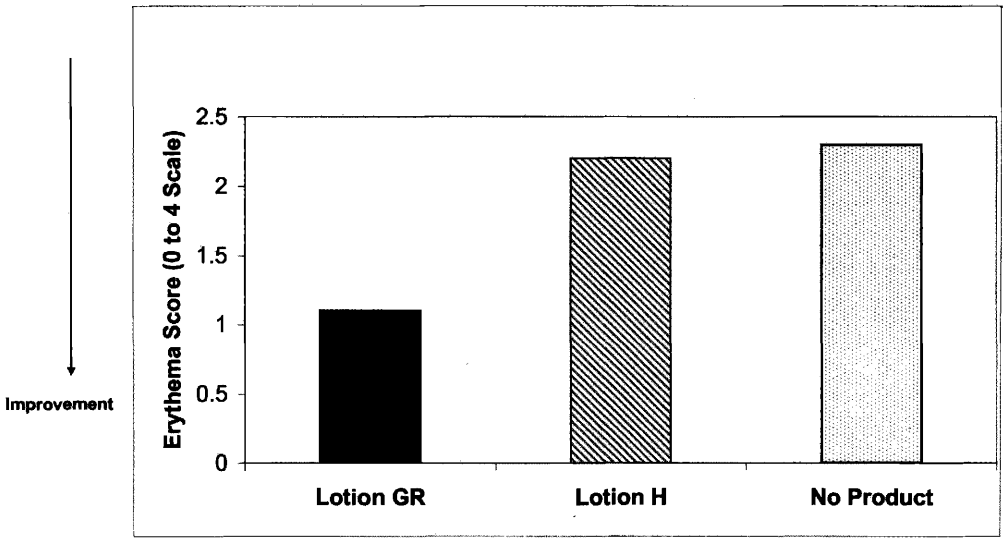


Figure 3. Prevention of primary dermal irritation. The ability of lotions to prevent surfactant-induced primary irritation was assessed by a trained observer evaluating erythema.

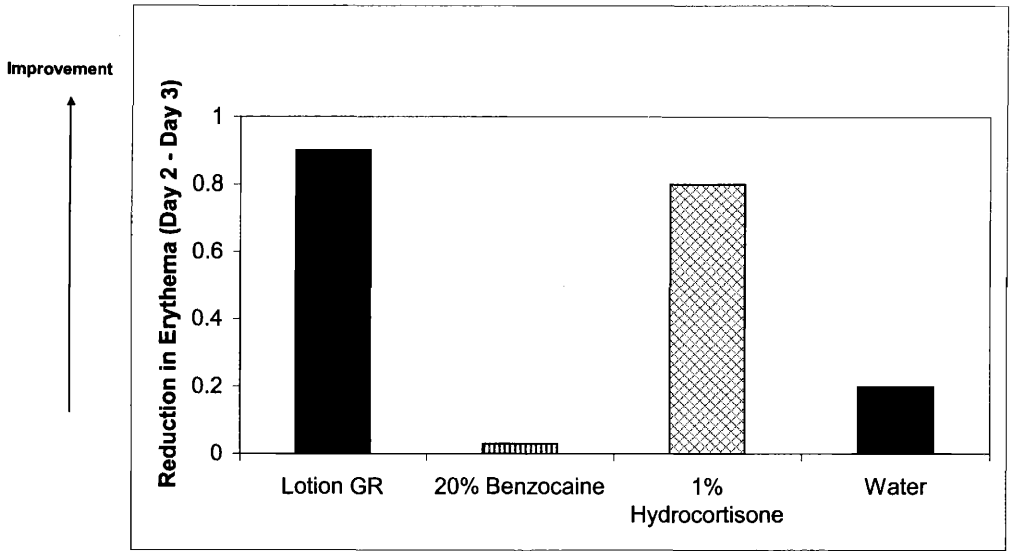


Figure 4. Alleviation of primary dermal irritation. The ability of lotion GR to reduce primary irritation caused by exposure to SLS was assessed by a trained observer evaluating erythema.

Overall dermatological assessment. After one and two weeks of use, lotion GR and associated products effectively decreased dry-skin scaling (see Figure 5a), excoriation, fissuring, crusting, erythema, lichenification, and roughness. Thus, they are valuable ancillary products in treating patients with mild-to-moderate xerotic eczema accompanied by itching.

Overall skin care product assessment (subject-assessed). Panelists reported that using Lotion GR and its associated cleansers produced statistically significant improvements in skin softness, smoothness, and moisturization, as well as in the appearance and feel of dry skin (Figure 5b). Additionally, participants reported a decrease in skin itching, roughness, and irritation. Thus, these products deliver panelist-recognizable skin benefits to those suffering from dermatoses accompanied by itching.

CONCLUSIONS AND DISCUSSION

In vivo controlled-use models allow for the evaluation of the different benefits of moisturizers in different situations, which lead to discrimination between moisturizers with different formulae. Based on the results of each *in vivo* model, it is concluded that moisturizers can reduce both primary irritation and dryness, as well as prevent their recurrence. However, some lotions are more effective than others; a lotion with a high concentration of glycerin was particularly effective. Additionally, results of the home-use study support the *in vivo* model findings and confirm the validity of this approach.

The ability of glycerin to alleviate both dryness and primary irritation is well established. Using the regression test, Shapiro (23) showed that glycerin was able to alleviate dry skin in a dose-dependent manner. Rawlings *et al.* (24) have recently confirmed this. There are several possible mechanisms by which glycerin may relieve dryness. Glycerin, an effective humectant, may absorb water from the underlying layers of the skin. An

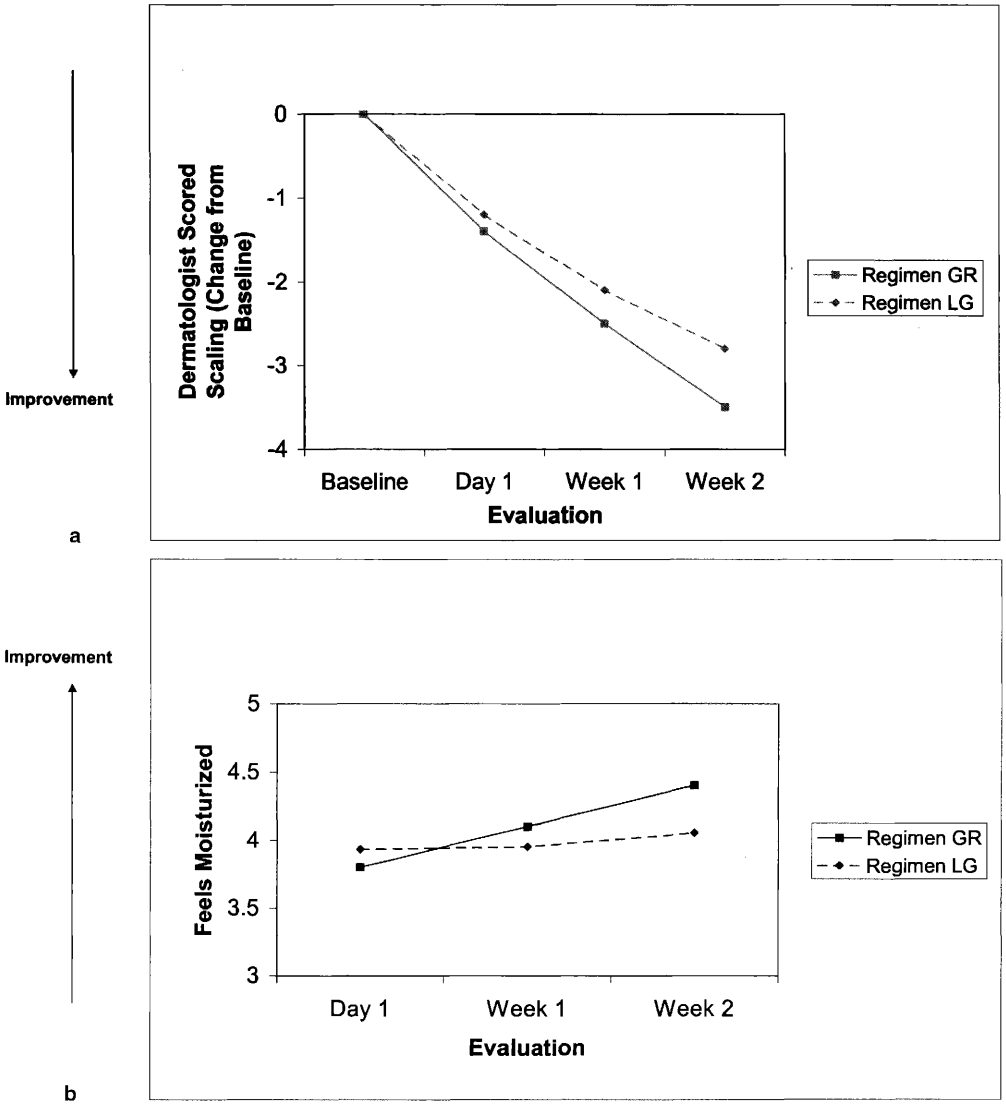


Figure 5. Results of the home-use validation study. The effects of different regimens on panelists' skin conditions were assessed in a home-use study. The panelists' skin was evaluated by (a) a dermatologist and (b) the panelists.

alternative mechanism that has been demonstrated *in vivo* is the stimulation of the enzymes that are responsible for proper desquamation (25). Another possibility proposed by Froebe, Mattai, and their colleagues (26,27) from *in vitro* studies is that glycerin can prevent the phase transition of stratum cornuem lipids from liquid crystal to gel phase even when the bilayer is partially dehydrated. This phase change in the lipid bilayer can result in an increase in water loss, and *in vivo* this may affect the stratum cornuem water barrier. These studies suggest that glycerin can work by a variety of different mechanisms. However, for many of these mechanisms to be realized, glycerin must be able to penetrate into the stratum cornuem. This does occur, with glycerin being delivered to

the epidermis at a rate of tens to hundreds of micrograms of glycerin/cm^2 from the test lotions LG and GR, respectfully, after 24 hours (data not shown).

Recently, glycerin has been demonstrated to be able to reduce irritation potential. Fluhr *et al.* (28) showed that glycerin accelerated the repair of the stratum cornuem barrier of human volunteers when tape stripping had disrupted the barrier. The recovery, compared with that of damaged but untreated skin, became significantly greater after three days and occurred whether the glycerin was applied openly or occluded to the damaged skin. Occlusion alone did not enhance recovery. Similar damage to skin was observed when washing with aqueous SLS solution, except that recovery appeared to take longer. However, the mechanism by which glycerin reduces irritation is not well understood. Mauro *et al.* (29) showed that barrier-function repair in mice occurs more rapidly at pH 5.5 than at 7.4. They speculated that the repair process involves extracellular lipid-processing enzymes, whose pH optima is somewhat acidic. It should be noted that the pH of lotion GR (at 4.5) was the lowest (most acidic) of the lotions tested.

Ultimately, it is important to demonstrate the relevance of controlled laboratory methods, whether *in vivo* or *in vitro,* to our consumers. This is the reason for running the home-use validation study. By using a group of consumers with a low level of dermatological distress (perceived itching, but few other clinical signs of eczema), we were able to show that a regimen based on using a high-glycerin lotion (GR) was significantly more effective than a regimen based on a low-glycerin lotion for both subjective and observable signs of eczema. This validates the predictions of the controlled *in vivo* studies.

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