

Review Article

Are we reaching the limits of our ability to detect skin effects with our current testing and measuring methods for consumer products?

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Testing for potential adverse skin effects is a key part of both the overall safety assessment for many consumer products and the evaluation of potential product improvements in mildness. Whilst modern tissue and paper products (i.e. facial tissues, catamenial products, baby wipes and baby and adult diapers) are inherently very mild to skin, current test methodology may not be robust enough to evaluate future improvements in such products. This article provides a commentary on several technologies we have been exploring to improve the sensitivity of test methods for tissue and paper products. The focus has been on three approaches: (i) further exaggerating exposure conditions using novel approaches to sample application, (ii) increasing the sensitivity of the manner in which we score for irritant effects, either visually or via instrumentation and (iii) quantitatively measuring additional endpoints, i.e. subjective sensory effects.

Key words: compromised skin, mechanical irritation, polarized light, sensory effects, skin irritation, visual grading. © Blackwell Munksgaard, 2005.

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Testing for potential skin effects is a key part of the overall safety assessment, and product claims support for many consumer products. The current approach employs exaggerating the concentration and duration of exposure using a variety of test protocols, including standard patch testing and extended product use tests, with expert clinical evaluation of erythema and dryness as a measure of irritation. For decades, this approach has served the consumer products industry well in detecting differences in potential skin effects (1–4). This approach has allowed for the precise assessment of product safety performance and provided support for product innovations that have enabled the consumer to benefit from continuous product improvements.

Modern products in the tissue and paper products categories (including facial tissues, catamenial products, baby wipes and baby and adult diapers) are inherently very mild to skin, and produce few adverse skin effects when tested even under very stringent conditions. However, recently, we have seen that current test methods may not be robust enough to evaluate perceived skin effects that may be important for consumer comfort during product use. This observation is consistent with feedback from consumers

obtained via our toll-free number, indicating that consumers develop product preferences based on perceived skin effects that are not always expected based on results of objective skin effects testing in the laboratory (non-published data). Further, sensory data collected from panelists participating in skin effects testing indicate that panelists can sometimes discriminate between products based on how they feel during use, even when clinically evaluated skin effects (erythema and dryness) show no differences. This has been observed, for example, when testing catamenial products in the behind-the-knee (BTK) test, and when testing facial tissues in a recently developed nasal irritation model (5, 6). Others have reported similar experiences in exaggerated use tests. Simion et al. (7) testing personal cleansing products in an exaggerated arm washing model, found that panelists' descriptions of sensations, i.e. dryness, tightness, itching, etc., yielded information on potential skin effects beyond the visible clinical observations.

These observations lead to the conclusion that our traditional skin testing approaches are not always good predictors of consumer-perceived skin comfort. Many of our recent efforts have been directed toward increasing our capabilities

to predict and quantify these consumer-perceived differences in comfort that are often undetected using the traditional skin test methods and assessment tools. We have been exploring three approaches: (i) further exaggerating exposure conditions, (ii) increasing the sensitivity of the manner in which we score for irritant effects, either visually or via instrumentation and (iii) quantitatively measuring additional endpoints, i.e. subjective sensory effects. Of course, any modifications or new methods must be cost effective, and should not significantly increase the level of panelist discomfort. This is a commentary on the progress we have made in these areas.

Further exaggerating exposure conditions

During use testing of consumer products, exposure conditions can be exaggerated by increasing the concentration of the product during testing or by increasing the duration of exposure. Neither of these approaches is practical for tissue and paper products, where products are intended for use undiluted, and where some products (catamenial products and baby and adult diapers) are intended to be worn in contact with the skin for prolonged periods of time. However, it is possible to exaggerate the conditions of use by increasing the mechanical irritation through friction at the test site, or by testing on skin that has been compromised by tape stripping or other means. Recently, we have conducted programs on 3 test methods that use one or both of these approaches.

The BTK test was developed specifically for catamenial products (8, 9). Samples are applied daily to the back of the knee using an elastic athletic band for 6 hr each day for 4-5 days. This sample application method results in increased mechanical friction compared to actual use conditions, with a resulting increase in the irritant reactions that develop. Irritation reactions are scored by visual assessment. The BTK test gives consistent and reliable results on different types of materials, from thin menstrual pad topsheets to tampons. Results from selected studies are summarized in Table 1. Comparisons to testing conducted at other body sites, such as the upper arm, axilla and wrist, indicated that the BTK test produced the most reliable results, with the greatest ease of sample application, and the least discomfort to the volunteer panelists (8). In addition, comparison of the BTK test results to in-use clinical tests conducted on the same materials indicate that the BTK test provides results that are consistent with the in-use clinical test in a shorter period of time and at a greatly reduced

cost. In addition, the BTK is easier to conduct for both investigators and panelists.

A nasal irritation model was developed to study potential skin effects of facial tissues (6). Like the BTK test, this model uses an application approach to increase the mechanical irritation over and above that which would be expected to occur during normal product use. In this system, panelists wipe the facial tissues (one on each side) from the nasal bridge to the upper lip for 10 wipes every 20 min for a total of 170 wipes (17 series) daily on Monday through Thursday. 4 areas of the nose were visually scored for erythema and dryness: the nasal bridge, nostrils, nasal-labial folds and the area underneath the nostrils. In a comparison of a lotioned facial tissue to a non-lotioned facial tissue, differences were observed between the test products at isolated timepoints. Interestingly, in response to specific questions on various sensory effects, panelists expressed product preferences statistically more significant than those detected by the objective measures for irritation, i.e. visibly scored erythema and dryness.

We are beginning experiments using an abrasion wheel device. This equipment uses a rotor, turning at speeds up to 100 RPMs, to lightly rub the skin. When a tissue or paper product is affixed to the surface of the wheel, the product can be evaluated for mechanical irritation effects. Reactions are scored visually, and via a Laser Doppler Scanner. Results will be the subject of a future publication.

The modified forearm-controlled application technique (modified FCAT) was developed to evaluate the relative mildness of several types of products, such as baby wipes, feminine hygiene products and facial tissues (10). Treatment consisted of 15-30 sec wipes on the forearm using the baby wipe product 4 times each day for 3-5 days. Reactions were evaluated by visual scoring and by instrumental scoring for transepidermal water loss (TEWL, using a ServoMed Evaporimeter EP1[®]) and erythema (using a Minolta Chromameter CR-200[®]). The method demonstrated consistent and clear product differences by all scoring methods. Results of a typical study are shown in Table 2.

Surprisingly, tape stripping skin test sites prior to exposure has not resulted in an increase in the ability of our test models to demonstrate differences in the potential irritant effects of our products. Tape stripping was used in the development stages of the BTK test described above, but did not increase the ability of the test to detect product differences compared to skin that had not had this pretreatment. In the nasal irritation test for facial tissues, tape stripping was performed

Table 1. Behind-the-knee (BTK) results on diverse product and material types

Exposure regimen	Number of panelists	Materials tested	Mean irritation score $\pm$ SE	Comments
6 h/day For 4 days	12	Burlap fabric Satin fabric	1.5 $\pm$ 0.17 0.6 $\pm$ 0.08	^b Expected result based on material characteristics
6 h/day For 5 days	16	Standard pad A Standard pad B	2.0 $\pm$ 0.14 1.4 $\pm$ 0.11	^a Expected result based on previous testing and marketplace experience
16 h/day For 5 days	11	Topsheet AT Topsheet BT	1.3 $\pm$ 0.25 0.59 $\pm$ 0.16	^a Expected result based on previous testing and marketplace experience
16 h/day For 5 days	14	Minipad AU Lotioned pad AUL	1.5 $\pm$ 0.17 1.1 $\pm$ 0.19	^a Expected result because a lotion coating would be expected to reduce mechanical irritation
6 h/day For 5 days	15	Tampon R Tampon S	0.90 $\pm$ 0.09 1.0 $\pm$ 0.10	^c Expected result based on the similarity of the two test products
6 h/day For 5 days	22	Intralabial pad IL-2 Pantiliner P	1.4 $\pm$ 0.09 1.4 $\pm$ 0.11	^c Expected result based on in-use clinical study results

Samples were applied daily to the back of the knee using an elastic athletic band for the specified number hours each day for 4–5 days. This method of sample application results in an increase in mechanical friction compared to actual use conditions, with a resulting increase in the irritant reactions that develop. Irritation reactions at the test sites were scored by visual assessment on a scale of '0' (no irritation) to '4' (severe irritation) 30–60 min after removal of the test samples. The mean irritation score for each product was determined and evaluated using stratified Cochran-Mantel-Haenszel (CMH) tests. Results were reproduced from Farage (2004) (9).

^aSignificant at <5%

^bSignificant at <0.02%

^cNS Not significant

on 1 of the 4 areas prior to treatment; the nasolabial fold. If tape stripping increased the sensitivity of the test, one would expect that product differences would show up more frequently at this site, compared to the other three sites that were not pretreated in this manner. However, few product differences were detected, and those that were evident occurred randomly at all 4 of the anatomical sites that were graded for erythema and dryness.

There may be several explanations why tape stripping has not increased the sensitivity of our

tests. One possible explanation may be that our tape stripping protocol was not vigorous enough. In our models, we used up to 20 repeated applications of tape. Bashir et al. (11), using TEWL to study barrier disruption in skin stripped multiple times, found that TEWL did not increase significantly after 10 or 20 tape applications. After 30 applications, TEWL had increased significantly on the dorsal surface of the forearm, but not the ventral surface. A significant increase on the ventral surface was observed only after 40 sequential applications.

Table 2. Comparison of Three Baby Wipe Products in the modified FCAT

Treatment	Early terminations ^a	Final visual scores		Final instrumental scores	
		Erythema	Dryness	Redness (a*)	TEWL (g/m ² h)
Untreated	0%	0.11 $\pm$ 0.24	0.15 $\pm$ 0.23	9.2 $\pm$ 1.2	3.16 $\pm$ 1.2
Product A	0%	0.30 $\pm$ 0.31	0.23 $\pm$ 0.26	9.4 $\pm$ 1.2	4.5 $\pm$ 1.6
Product C	14%	1.28 $\pm$ 0.89 ^b	0.51 $\pm$ 0.29 ^c	10.8 $\pm$ 1.6 ^d	10.7 $\pm$ 4.8 ^d
Product D	46%	2.13 $\pm$ 0.92	0.62 $\pm$ 0.34	12.5 $\pm$ 1.9 ^e	15.9 $\pm$ 7.1 ^e

Treatment consisted of 15–30 sec wipes on the forearm using the baby wipe product 4 times each day for 5 days. Reactions were evaluated by visual scoring on a scale of '0' (no irritation) to '4' (severe irritation) and by instrumental scoring for transepidermal water loss (TEWL, using a ServoMed Evaporimeter EP1[®]) and erythema (using a Minolta Chromameter CR-200[®]). Data for the final scores on the final day are given above (mean $\pm$ SD). 31 panelists completed the study. Results were reproduced from Farage (2000) (10).

^aThe washing procedure was terminated due to a visual score of ≥ 3 at the test site.

^bSignificantly different from Product A ($P < 0.0001$) using Wilcoxon's matched pairs test.

^cSignificantly different from Product A ($P < 0.001$) using Wilcoxon's matched pairs test.

^dSignificantly different from untreated control, and Products A and D ($P < 0.01$) using Tukey's protected *t*-test.

^eSignificantly different from untreated control, and Products A and C ($P < 0.01$) using Tukey's protected *t*-test.

Another possible explanation why tape stripping may not have had an impact on the sensitivity of our tests may be the specific tape being used. Different tape adhesives may have different affinities for materials within the stratum corneum, leading to potential differences in the impact of tape stripping. Schwindt et al. (12) proposed that water diffusion through the stratum corneum is determined by the intercellular lipids and that the corneocytes are minimally permeable. Thus, use of a tape with an adhesive that has a high affinity for lipids may result in an increased permeability for hydrophilic materials. Conversely, use of a tape with adhesive that has a low affinity for the intracellular lipids may lead to removal of corneocytes and an increased permeability to hydrophobic materials.

There is also evidence that pretreatment to compromise the barrier function of the skin may lead to a reaction that is not typical of the classical irritant response. Gebhard et al. (13) used a number of pretreatment protocols prior to application of SLS. These included: (i) none, (ii) pricking with a Lancet, (iii) pricking with a TB test stamp, (iv) scarification with a Lancet and (v) incision scratching. Interestingly, the site with no pretreatment produced the highest clinical scores for irritation reactions. Further, there was a qualitative difference between the reactions produced with either no pretreatment or with the first 2 pretreatment protocols (i.e. treatments i–iii, above) compared to the latter 2 pretreatment protocols (treatments iv–v). The proposed explanation was that the more aggressive pretreatments produced reactions in the deeper layers of the epidermis that did not reflect the reaction that occurs with a topically applied irritant. Granted, tape stripping compromises the stratum corneum in a way that is different from puncturing or incising the epidermis. However, such results would suggest caution when using skin-compromising pretreatment techniques in the development of test models for consumer products intended for use on intact, healthy stratum corneum.

Increasing scoring sensitivity (visually and/or via instrumentation)

Visual scoring represents the cornerstone of skin irritation testing, and trained skin graders can accurately and reproducibly score test sites for erythema and dryness. Griffiths et al. (14) conducted an intralaboratory comparison of results from patch testing using standard irritants. By necessity, different graders were used. There was excellent correlation between results obtained at the different laboratories. Several authors have

demonstrated that trained graders can reliably detect evidence of irritation with equal or higher degrees of sensitivity to that of instrumental measures (15–19). Results from our own laboratory indicate that visual scoring yields results that are as reliable as measures of TEWL or of erythema via chromameter.

It's possible that the design of many current test models is not optimum to detect early subclinical changes in the skin. Current test methods were developed to result in a grader being able to see a reaction. However, physiological changes that occur early in the process of irritation, such as changes in blood flow, moisture content, pH, etc., would be expected to occur before any reaction is visible. In other words, by the time the reaction is visible, it may be too late to measure the early changes in skin physiology. These early changes may be key to our ability to distinguish subtle skin effects and, therefore support future product development efforts. However, in order to see these early changes, investigators must either design a different type of test, or use non-irritating materials in existing tests.

Reports from some authors support this notion. In the examples given above, visual scoring of irritant reactions was equally or more reliable than some instrumental methods (15–19). However, some investigators have described measurable changes in skin characteristics after treatment with materials that produce very little or no visible reaction. In patch testing using moisturizer formulations, Agner et al. (20) scored reactions for redness (visual), TEWL, blood flow (via laser Doppler) and hydration (via electrical capacitance). Test sites were scored prior to patching, after 1, 24-hr patch (day 1), and after 2, 24-hr patches (day 2). Reactions at test sites were compared to a positive control (SLS) and negative control (empty patch chamber). They showed detectable differences in skin hydration and blood flow, but nothing detectable by TEWL or visual scoring. Tupker et al. (21) evaluated the irritant properties of 6 antiseptics using twice daily open exposures. Reactions were evaluated by visual scoring, subjective irritancy scoring, skin hydration, TEWL and laser Doppler. All evaluation methods identified the same 2 antiseptics as the most irritating. However, the rank order for the other 4 materials varied depending on the scoring method. In this example, different instruments were likely measuring different physiological parameters that may not have been reflected in the visible signs of irritation.

Several methods are available to quantify various changes in skin physiology that may occur early in the irritation process or in the case of subclinical

reactions. Many of these have been reviewed recently by Berardesca et al. (22). In our laboratories, we have been investigating several for possible use in our skin effects testing.

An area of investigation, we have undertaken recently is instrumental enhancement of visual scoring through the use of polarized light. In this method, the skin is examined using parallel-polarized light, which illuminates surface detail, and cross-polarized light, which allows examination of subsurface details, such as the vasculature (23). Authors have described the use of polarized light as an aid in visualizing various skin conditions, including acne vulgaris, rosacea, photo-ageing, lentigo simplex and basal cell carcinoma (24–26). Recently, we have conducted preliminary experiments using a system which allows the visualization of the skin using both parallel- and cross-polarized light. Results will be reported in future publication.

Another area we have explored is the measurement of cytokines. Because cytokines are important mediators of inflammation, the ability to quantify changes in cytokine levels could provide important markers for the inflammatory process. We used a tape absorption method to isolate and quantify the presence of cytokines in normal skin, as well as in skin that was compromised by diaper or heat rash, sun exposure, or treatment with a chemical irritant (SLS) (27). Cytokines were collected via a 1 min application of Sebutape[®], extracted from the tape using saline, and evaluated using immunoassay techniques. Extracts were analysed for total protein and for the cytokines IL-1 α , IL-1RA and IL-8. In skin that was effected by diaper or heat rash, we saw significant increases in IL-1 α levels (determined as a percentage of total protein) compared to uninvolved skin. In sun exposed skin, we found significant increases in the IL-1RA/IL-1 α (3-fold to 6-fold) compared to skin that typically receives minimal sun exposure. In skin treated with SLS, under conditions which caused a minimal visible irritation reaction, we saw significant increases in IL-1 α levels, directional increases in IL-8 levels and significant decreases in the IL-1RA/IL-1 α ratio.

Instrumental measures of barrier function (TEWL) and redness (via chromameter) have demonstrated little advantage over visual scoring in our test systems. As mentioned above, both methods were used in the modified FCAT. Results were similar to those obtained with visual scoring. Other investigators have had similar experiences, as mentioned in the previous sections of this article. In addition to use in the modified FCAT, we have tried TEWL on a

number of body sites. The necessity for equilibration in a temperature and humidity-controlled room prior to the measurement increased the complexity of our scoring process, while providing no real advantage.

Quantitatively measuring additional endpoints, that is sensory effects

Sensory effects have been a critical area of investigation for some time for cosmetic preparations, where unpleasant sensations during product use can be a determining factor in consumer dissatisfaction. Recently, we have developed an increasing interest in using sensory effects in evaluating other types of consumer products (5, 6). As mentioned in some of the examples above, several investigators have described test results, where panelists are able to differentiate between different products based solely on sensory effects.

Measuring sensory effects in tests for skin irritation is developing increasing importance, especially for subclinical reactions. Green reviewed some important considerations in designing tests to quantify sensory effects, including the use of the labelled magnitude scale (28). Robinson subsequently used this scale to evaluate subject responses in chemosensory skin irritation studies using lactic acid and capsaicin (29).

Adding quantitative measures around sensory effects to our current test protocols may provide a potentially valuable tool for us to increase our abilities to detect product differences. Although our current test methods have not been optimized for this endpoint, we have begun to evaluate sensory effects in a number of recent studies.

In the BTK test mentioned above, panelists were asked questions on specific sensations they experienced at the test sites; sensations such as burning, itching, sticking, etc. (8). We determined that the product that was more irritating based on objective scoring also produced a higher number of certain skin complaints from the panelists. In addition, the mean irritation scores for the skin test sites where panelists complained of certain sensory effects was significantly higher than for those sites where the panelists did not have the specific complaint. This result is illustrated in Table 3.

We correlated the panelists' sensory experiences in 2 BTK tests with data generated as part of the routine product development process, i.e. the descriptive analysis panel (DAP) (5). This panel is a means of evaluating positive and negative physical characteristics of materials being considered for use in certain products intended to come into contact with the skin, such as diapers and catamenial products. In the DAP,

Table 3. Analysis of perceived sensory effects *versus* irritation scores in the behind-the-knee (BTK)

Sensory effect	Study 1			Study 2		
	Mean irritation score			Mean irritation score		
	Complaint reported by panelist	Complaint not reported	Regression results (<i>P</i> -value)	Complaint reported by panelist	Complaint not reported	Regression results (<i>P</i> -value)
Burning	1.70	1.50	0.069	1.82 ^b	1.50	<0.001
Sticking	2.25 ^b	1.52	0.059	1.75 ^b	1.54	0.001
Pain	1.88	1.52	0.155	1.78 ^b	1.57	0.019
Itching	1.52	1.53	0.938	1.70 ^a	1.58	0.148
Rubbing	1.52	1.53	0.949	1.67 ^a	1.58	0.187
Chafing	1.33	1.54	0.308	1.65	1.58	0.356
Other	1.46	1.53	0.613	1.79 ^b	1.58	0.040
Edema	none reported	NA	NA	1.17 ^b	1.60	0.008

The studies were conducted as described in Table 1. The mean irritation scores were determined for all test sites where the sensory effect was reported by the panelist, and for all sites where the effect was not reported. Significant differences between the means are indicated (^a*P* ≤ 0.10, ^b*P* ≤ 0.05). Irritation scores were then evaluated *versus* reported sensory effects using logistic regression, i.e. the presence/absence of a particular skin complaint was regressed against the irritation scores. Burning and sticking showed a relationship to the irritation score in both experiments. Pain and other (non-specified) complaints showed a relationship to the irritation score in Study 2. The reported complaint of oedema showed an inverse relationship to the irritation score. Results were reproduced from Farage (2001) (8).

specifically trained individuals grade products on characteristics such as scratchiness, cottony feel, plastic feel, smoothness, etc. In 1 product comparison, where visual scores and sensory scores produced a clear differentiation between the 2 products, we found a correlation with the DAP results for those 2 products. In 2 comparisons of 2 products, we found mixed results in visual scores, sensory scores and DAP results.

Like the BTK studies, the nasal study on facial tissues mentioned above was not designed to optimize the ability to detect differences in sensory effects (6). Nevertheless, the panelists expressed a clear preference for the lotioned product over the non-lotioned product based on a number of sensory effects endpoints, even though only small differences were observed in the visual measures of irritation.

Conclusion

Current test methods have been used successfully for decades to detect differences in potential skin effects in the course of product development activities and claims support. Our challenge for the future is to use all potential tools in our arsenal for developing more sensitive test methods capable of detecting skin benefits and very subtle improvements in the potential for adverse effects. These tools include seeking ways to further exaggerate exposures, enhancing the ability to clinically score for the endpoint of irritations, either visually or via instrumentation and finding new scoring endpoints, such as subjective, sensory effects.

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