

Review Article

Sensory, clinical and physiological factors in sensitive skin: a review

MIRANDA A. FARAGE¹, ALEXANDRA KATSAROU² AND HOWARD I. MAIBACH³

¹The Procter & Gamble Company, Winton Hill Business Center, Cincinnati, OH, USA, ²University of Athens Medical School, Department of Dermatology, Athens, Greece, and ³University of California-San Francisco, CA, USA

Certain individuals experience more intense and frequent adverse sensory effects than the normal population after topical use of personal care products, a phenomenon known in popular usage as sensitive skin. Consumer reports of sensitive skin are self-diagnosed and often not verifiable by objective signs of physical irritation. Companies who manufacture cosmetic and personal care products are challenged to provide safe products to an audience with tremendous differences in skin type, culture and habits. This review examines the still incomplete understanding of this phenomenon with respect to aetiology, diagnosis, appropriate testing methods, possible contributing host factors such as, sex, ethnicity, age, anatomical site, cultural and environmental factors, and the future directions needed for research.

Key words: age; anatomical site; barrier function; environmental factors; ethnicity; irritation; sensitive skin; TEWL; vulva. © 2006 The Authors. Journal compilation © 2006 Blackwell Munksgaard.

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The term *sensitive skin* – of lay origin (1) – commonly refers to an exaggerated and unpleasant sensitivity of the skin to frequent or prolonged use of everyday products such as cosmetics or toiletries (1). Epidemiological surveys show a high prevalence. In a phone survey of 800 ethnically diverse women in the US, 52% professed sensitive skin, with no statistical difference between ethnic groups (2). In a UK mail survey of 2058 people (both men and women), 51.5% of the women and 38.2% of the men reported sensitive skin as well (3).

Researchers have largely ignored consumer reports of sensory irritation because they are both difficult to quantify and frequently (50%) unaccompanied by visible signs (4). The reactions, however, are ubiquitous and globally dispersed and demand a clinically satisfactory understanding. The question is not merely academic. Before introducing any new product into the marketplace, both skin safety testing and risk assessment are performed to insure skin compatibility under a variety of potential exposure conditions (5). Consumer sensitivity is commercially critical as well because, though largely sensory without obvious physical effect, it strongly influences consumer choice (6). In fact, 78% of consumers who profess sensitive skin report avoiding

some products because of unpleasant sensory effects associated with their use (2).

Definition and Classification of Sensitive Skin

The term *sensitive skin* needs to be precisely defined. A tenuous consensus in the literature is that sensitive skin is characterized by subjective complaints of discomfort without predictable classical visible signs of irritation (7) and without an immunologic response (7, 8). Although transient redness, dryness or tenderness may accompany adverse sensations (8), and sensitive skin may be less supple or hydrated (9), subjects often experience sensory effects only (8). Subjective irritation (9), invisible irritation (4), non-immunologic adverse skin reactions (1), non-immunologic inflammation and self-estimated enhanced skin sensitivity (10), have been proposed as more clinically meaningful terms.

It is believed that some subjects report greater incidence of adverse reactions to certain products because of higher sensitivity (1–3, 5, 9). Some individuals possess exaggerated sensitivity to specific individual irritants (11). Despite the fact, however, that some studies have demonstrated that sensitive-skin patients are capable of distinguishing products based on blinded sensory

endpoints (1, 12), a clinically satisfactory description of observed sensitivities is still out of reach.

Progress in defining sensitive skin has been hampered by various issues. The condition is typically self-diagnosed (7) and there is no agreement, beyond heightened sensitivity, on its symptoms (1). Its presentations include stinging, itching, burning, dryness, erythema, desquamation, papules, wheals and scaling (1, 13) which occur over a wide range of intensities (8). To further complicate the diagnosis, cutaneous irritation is a syndrome with multiple potential factors (7) such as age, genetics, hormonal factors, skin dryness, race, skin pigmentation, anatomic region, pre-existing diseases, cultural factors and environmental factors (4).

Another challenge in the proper identification of the appropriate target population is finding the best testing methods. Many people who profess sensitive skin do not predictably experience visible signs of the sensations reported, whereas some who describe themselves as non-sensitive react strongly to tests of objective irritation (14). In one study, an irritant dose that was completely tolerable in 99 subjects caused pronounced irritation in the hundredth; and in another study (which tested a three-irritant panel in 200 subjects), 197 subjects reacted to at least one of three irritants, whereas three subjects did not respond at all (15). In addition, the severity of individual responses to irritants tested varied tremendously (16), even among chemicals with similar modes of action (1).

Testing has showed sizeable variation within the same individual at different anatomic sites (16), and even at the same anatomical site on symmetric limbs. In a test of irritant response to the surfactant sodium lauryl sulfate (SLS) in an aluminium patch test, e.g. the right and left arms differed significantly in 47% of individuals tested (17). Also, the methodology used may introduce additional variability, as in a similar SLS patch test utilizing a Finn Chamber[®], 84% tested identically on the right and left arm (17).

Most methods have focused on objective assessment of physical effects to skin rather than the sensory effects reported (12), and most test protocols have relied on exaggerated exposure (5) of uncertain relationship to actual consumer use (1). In addition, most actual testing has included very few subjects, although few have restricted subjects to those with demonstrated sensitivity (5).

It is likely that the phenomenon of sensitive skin, when unraveled, will prove to be an umbrella classification comprised of distinct subgroups of clinical sensitivities. Pons-Guiraud has

proposed three subgroups as follows: *very sensitive* skin, reactive to a wide variety of both endogenous and exogenous factors with both acute and chronic symptoms and a strong psychological component; *environmentally sensitive*, comprised of clear, dry, thin skin with a tendency to blush or flush and reactive to primarily environmental factors and *cosmetically sensitive* skin, transiently reactive to specific and definable cosmetic products (7). Muizzuddin et al. defined three subgroups somewhat differently. His classifications include *delicate skin*, characterized by easily disrupted barrier function not accompanied by a rapid or intense inflammatory response; *reactive skin*, characterized by a strong inflammatory response without a significant increase in permeability and *stingers*, characterized by a heightened neurosensory perception to minor cutaneous stimulation (18).

Methods Applied in Clinical Studies

Researching sensitive skin has employed a variety of methodological approaches. Chemical and mechanical irritants of numerous types and mechanisms have been employed, and numerous methods of assessing reactivity have been devised. Methods can largely, however, be broken down into those that assess neurosensory response (sensory reactivity tests), those that assess visible cutaneous signs of irritation (irritant reactivity tests) and those that measure structural and physiological parameters of the skin for indications of irritant effect (dermal function tests) (Table 1).

Sensory reactivity tests

Sensory reactivity tests focus on the neurosensory component of the sensitive skin response. The most popular has been the sting test (19), in which lactic acid (although other agents including capsaicin, ethanol, menthol (1), sorbic acid and benzoid acid (9) have also been employed) is applied to the skin. Tape stripping, a procedure that removes the stratum corneum, is sometimes performed before irritants are applied (20).

The irritant is typically applied to the nasolabial fold, an area considered highly sensitive because of a permeable horny layer, a high density of sweat glands and hair follicles, and rich innervations (Fig. 1) (8, 21). Sensory feedback is collected and typically quantified by a labelled magnitude scale (13). Although the sting test is considered to be the best approach to defining a potentially susceptible population (1), it has not proven predictive of sensitivity to other irritants

Table 1. Methods for evaluating sensitive skin

Objective of test	Parameter measured and most common irritant	Assessment methodology	Advantages	Disadvantages
Sensory reactivity tests To provide measure of perception of pain in absence of visible irritation	Stinging sensation with lactic acid as most common irritant	Sensory perception questionnaire typically utilizing point scale	Very quick, easy and inexpensive Requires no instrumentation	Often non-reproducible Lacks objective criteria Relationship to objective measures of irritation undefined
Irritant reactivity tests To provide measure of visible sequelae to irritant exposure (typically dryness or erythema)	Objective cutaneous irritation with SLS as most common irritant	Visual scoring (measures skin irritation by visual inspection) LDV (measures skin irritation by blood flow)	Relatively inexpensive & quick Requires no instrumentation Non-invasive Objective Quantitative Biomechanical assessment	Often non-reproducible Not objective Relationship to neurosensory perception undefined Requires expensive instrumentation Indirect measure, less sensitive than TEWL Defines negative and positive reactions but does not quantify differences in positive reactions well Some irritants (NaOH, dithanol) do not cause measurable response Requires expensive instrumentation Indirect measure Less sensitive than TEWL
To provide evaluation of water loss in skin not attributable to sweating	TEWL (barrier integrity) with SLS as most common irritant	Colour reflectance (measures skin irritation by minute colour change)	Non-invasive Objective Accurate Reproducible Allows quantitative comparison of erythema both within and between individuals Quantitative Best measure of skin damage	Requires expensive instrumentation Requires stringent conditions Easily confounded by temperature, humidity, host factors
To provide measure of water content of the skin by assessment of a dielectric constant	Skin hydration with SLS as most common irritant	Evaporimeter (closed chamber, open chamber, and ventilated chamber) Electrical capacitance, Corneometer®	Quantitative Relatively quick	Defines arbitrary units, difficult to standardize, assumes <i>ceteris paribus</i> Confounded by skin surface features and salt content Little correlation with irritant testing
Structural sensitivity tests To provide evaluation of structural alteration of skin as a result of exposure to cutaneous irritants	Skin thickness with SLS as most common irritant	Ultrasound Light microscopy	Quantitative, relatively quick Highly accurate Non-invasive, suitable for any anatomical site Quantitative	Requires expensive instrumentation Labor-intensive

Table 1. Continued

Objective of test	Parameter measured and most common irritant	Assessment methodology	Advantages	Disadvantages
To provide assessment of alteration of skin permeability as a result of exposure to cutaneous irritants	Skin penetrability with SLS as most common irritant	Confocal light microscopy	Requires no specialized equipment Highly accurate	Histological preparations subject to artifacts Invasive, not suitable for all anatomical sites
			Quantitative, accurate Allows direct measurement on unmodified skin Allows assessment of skin beyond surface depth Correlates well with skin sensitivity	Requires specialized expensive equipment
		UV light		Requires specialized expensive equipment

LDV = laser Doppler velocimetry; NaOH = sodium hydroxide; SLS = sodium lauryl sulphate; TEWL = transepidermal water loss; UV = ultraviolet.



Fig. 1. The nasiolabial fold, an area considered highly sensitive because of a permeable horny layer, a high density of sweat glands and hair follicles, and rich innervation.

(21). It does have the advantage of being simple, quick and relatively inexpensive to perform, producing a mild, transient response without visible effect.

Although reports in the literature are relatively few, the innervation of the dermis and epidermis have also been evaluated for physiologic differences that could explain heightened sensitivity, typically by staining neural tissue with compounds that illuminate specific components of the neurosensory network (22).

Irritant reactivity tests

Irritant reactivity tests attempt to measure objective signs of irritation. The SLS method has been the most common. A common ingredient of many cosmetics and other personal care products, SLS is an anionic emulsifier with an irritant potential at a concentration of greater than 1% or less (17). SLS modulates surface tension, alters the stratum corneum (17), increases blood flow (17) and enhances skin permeability (17). It is a primary irritant, which damages skin by direct cytotoxic action, without prior sensitization (17).

SLS as well as other potential irritants has been applied in patch tests (1) including, chamber-facilitated patch tests (5, 10, 17, 18) and repeat insult patch tests (14, 18, 23), open application tests (17, 18), soak or wash tests (17) and plastic occlusion stress tests (17).

Irritant testing has often employed exaggerated exposure (4, 13), with a demonstrated capability of achieving product differentiation (4). Newer versions of the approach exaggerate effects by adding a frictional component (13). These protocols, however, are not applicable to paper or tissue products, and many modern products

produce few effects even under exaggerated conditions. Interpretative caution must be exercised as well. Even physiological saline can cause irritation with extended occlusive application (23), and real-life exposure is typically short-term, not occluded, and cumulative (17).

Other irritants employed have included dimethyl sulfoxide (1), benzoic acid, *trans*-cinnamic acid (1), acetic acid (5), octanoic acid (5), decanol (5), sodium dodecyl sulfate (1) and vasodilators (24). Mechanical irritation testing has evaluated facial tissue (20) and sanitary pad surfaces (11).

Reactivity to SLS and other irritants is frequently visually scored to obtain clinically graded assessments of erythema and oedema (8, 25). Erythema has also been measured by cutaneous blood flow (10, 26) plethysmography (17) and colour reflectance (9). Laser Doppler velocimetry (LDV) measures cutaneous blood flow, indirectly evaluating penetration of vasoactive substances as a measure of permeability (26). Colour reflectance measures slight changes in colour within three values of hue (17). A correlation between skin colour by this method and SLS dose has been demonstrated (9, 17), although one author reported no correlation (17), as well as a correlation with visual erythema scoring (17). Both techniques offer a non-invasive (27), objective assessment of a subclinical skin process without external visible effects (13). When testing the irritant potential of vasodilators, however, LDV and colour reflectance are an indirect measure dependent on vasodilation as the final endpoint of a five-step physiological process (27).

Visual scoring of irritancy in the vulva has demonstrated that the area reacts less intensively and recovers faster than does exposed tissue (28). Objective assessment by LDV, unfortunately, has been demonstrated to be less sensitive in that anatomical area (27). Available bioengineering techniques for quantifying irritation have, in general, proven less suitable in the vulvar area than in other body regions (28).

Dermal function tests

Structural sensitivity tests measure structural or physiological changes that may be associated with the neurosensory responses in sensitive skin. Transepidermal water loss, or TEWL, measures skin surface water loss (29), as a measurement of the integrity of barrier function (30), and therefore quantify skin damage (16). TEWL is considered an indicator of the functional state of the stratum corneum (29), and has proven to be a better measure of irritant susceptibility than

clinical visual scoring (16). It is considered the single best measure of skin sensitivity; a high baseline TEWL was defined by one author as 'the' diagnostic criteria (17). TEWL measurement has demonstrated a positive SLS dose–response curve for skin response (17) and TEWL baseline measurements have proven to be correlated with sensitivity to SLS (31). When compared with LDV, ultrasound and colour reflectance, TEWL was found to be best correlated with SLS exposure (17).

TEWL measurement is often accompanied by tape stripping, a procedure which does not guarantee removal of the stratum corneum and which, when successful (13), no longer tests the effect on normal skin (13). TEWL is also easily affected by endogenous factors such as cutaneous blood flow, diurnal rhythm, eccrine and sweat gland density (29), and it requires temperature and humidity control for meaningful results (13).

Skin hydration, typically assessed by electrical capacitance, is characterized by significant individual variation (17) and is heavily confounded by skin surface texture or density of hair (32). Results have not correlated well with irritant patch testing (17). Hydration can also be assessed by corneometer (10) and is sometimes expressed by desquamation index (33).

Skin thickness has been measured by ultrasound (17). Ultrasound measurements after SLS exposure correlate well with TEWL assessment of barrier function (17). Light microscopy with cyropreservation, however, is a more accurate assessment of epidermal thickness (34). Skin penetration by ultraviolet (UV) light is dependent on both thickness and the structural composition of the skin. Cutaneous sensitivity to UV light was found to have positive correlation with skin sensitivity to a seven-irritant panel, especially as compared with traditional classification of skin type, which was less reliable (17).

Future needs in method development

The usefulness of any particular technique depends on the relative and actual degree of changes present (28). Effective methodology could be defined as that in which sensitive patients successfully and consistently discriminate between products (35). Traditional testing has not achieved that goal, or the ability to predict universal sensitivity (13). Useful methods will need to be cost effective, reproducible and minimally invasive (13). Instrumental enhancement of visual scoring through polarized light (13) and assessment of cytokine levels as a measure of sub-clinical tissue damage are being planned (13).

Relationship between Irritant Stimulation and Sensory Response

A subgroup of sensitive subjects, termed 'stingers', display stronger sensory irritation to chemical probes for stinging and burning (11) and that some subjects have higher erythematous responses to applied irritants (11).

Although initial studies observed an increased susceptibility to general irritation among 'stingers' (19), most research that followed found no correlation (1, 8). Strong reactivity to one non-immunologic urticant has also failed to predict response to other urticants (1). There is significant disparity, in fact, between the severity of self-reported symptoms and the presence and/or strength of any objective signs (12), and few reports show correlation between sensory effects and objective endpoints (12).

Of the two studies reviewed that did evaluate the relationship between neurosensory responses and objective clinical irritation and included only subjects with demonstrated sensory sensitivity, both showed a correlation between sensory and objective signs. In a study regarding sensitivity to facial tissue which did not exclude non-sensitive individuals, sensory effects, in fact, were demonstrated to be the most reliable measure of product differences (20).

Although no predictive value was demonstrated for any individual sensitivity when subjects were tested with a seven-irritant panel, a weak association between tests was demonstrated by statistical analysis of binomial probability (1). However, studies, which evaluated the association of barrier function and sensitivity have yielded arguably the most conclusive results. A high baseline TEWL was associated with increased susceptibility to numerous cutaneous irritants by numerous studies and a variety of assessment methods (17).

Host Factors Affecting Skin Sensitivity

Numerous potential host factors (summarized in Table 2) undoubtedly play a role in experimental variability observed in sensitive skin. Basic differences are evident from epidemiological studies. This segment summarizes the findings on the effect of sex, race, age, anatomical site, culture, environment and other possible factors on skin sensitivity.

Sex

In general, women seem to complain of sensitive skin more often than men (6), although no sex differences were observed with respect to

Table 2. Host factors thought to promote sensitive skin

Factor	Reference
Female sex	Willis et al. (2001) (3)
Youth	Cua et al. (1990) (16)
Hormonal status	Britz et al. (1980) (48)
Cultural expectations in technologically advanced countries	Loffler et al. (2001) (10)
Fair skin which is susceptible to sunburn	Farage and Stadler (2005) (11)
Susceptibility to blushing and/or flushing	Willis et al. (2001) (3)
Skin pigmentation	Berardesca and Maibach (1988) (32) Robinson (2000) (5) Aramaki et al. (2002) (36)
Thin stratum corneum	Freeman et al. (1962) (49) Thomson (1955) (57) Pons-Guiraud (2004) (7) Johnson and Corah (1963) (50)
Decreased hydration of stratum corneum	Corcuff et al. (1991) (51) Loffler and Effendy (1999) (30)
Disruption of stratum corneum	Pons-Guiraud (2004) (7) Marriott et al. (2003) (39)
Increased epidermal innervation	Aramaki et al. 2002 (36)
Increased sweat glands	Lampe et al. (1983) (52)
Increased neutral lipids and decreased sphingolipids	Seidenari et al. (1998) (9) Reinertson and Wheatley (1959) (53) Brod (1991) (54) Elias and Menon (1991) (55) Schwarzendruber et al. (1989) (56)
Decreased lipids	Lee and Maibach (1995) (17)
High baseline TEWL	

TEWL = transepidermal water loss.

reactivity to 11 different tested irritants, including SLS (16). The thickness of the epidermis was observed to be greater in males than in females ($P < 0.0001$) (34), and hormonal differences which may produce increased inflammatory sensitivity in females have also been demonstrated (17, 41).

Ethnicity

Racial differences, with regard to skin susceptibility to irritants, are among the fundamental questions in dermatotoxicology (5). Two large epidemiological studies reported no observed racial differences in reporting product sensitivity (2, 3). Most testing, however, has focused on Caucasian females (5).

Differences have been observed in sensory perceptions, although substantive conclusions are hard to provide. Asians have been reported to complain of unpleasant sensory responses more often than Caucasians (36), supported by

the observation that a higher incidence of drop-outs in a Japanese clinical study withdrew because of adverse skin effects as compared with those in Caucasian studies (36). There have also been reports of an increased sensory response (36), as well as speed of response (36) in Asian subjects versus Caucasian in sensory testing (36). Another study, however, found fair-skinned subjects who are prone to sunburn had higher sensory responses to chemical probes than those with darker skintones (11). No racial differences in innervation on an architectural or biochemical level have been observed (1).

Studies of racial differences with regard to irritants have yielded conflicting evidence. Although black skin was demonstrated to have greater potential for irritant susceptibility than white skin (16), while another study found blacks to be less reactive than Caucasians (15). Asians seemed to be more reactive than Caucasians in some studies, and less in others, even within studies done under the same investigator and protocol (5). Tristimulus colorimeter assessment of skin reflectance observed that skin pigmentation was inversely associated with susceptibility to irritation (17), supported by the finding that irritant susceptibility to SLS is decreased after ultraviolet B (UVB) exposure (tanning) (17).

Methyl nicotinate assessment of vasoactive response suggests that there may be genuine racial differences in permeability (26). Increased percutaneous absorption of benzoic acid, caffeine and acetylsalicylic acid was demonstrated in Asians when compared with Caucasians (36), and decreased percutaneous absorption was observed in blacks (36).

Some structural differences with the potential to influence permeability have also been observed. Epidermal thickness was found correlate with pigmentation ($P = 0.0008$) (34), but not classical skin type (34). Tendencies to blush or flush are associated with both fair skin and a tendency to sensitivity (3), implying barrier impairment and increased vascular reactivity (3).

Blacks and Asians were shown to have higher baseline TEWL values than Caucasians (26). Although no significant differences in barrier function (Asian versus Caucasian) were observed (36), differences in ceramides between races have been observed (32, 36), as has a difference in the buoyant density of the stratum corneum (7). The number of sweat glands in the skin has been proposed as an influencing factor in permeability (36), and a huge variation in distribution and size of apocrine glands among races has been observed (36). Melanosomes of blacks have also been observed to be dispersed, whereas in

Caucasians and Asians they are membrane-bound aggregates (32).

Skin hydration has been observed to be higher in blacks, Asian and Hispanic subjects than in Caucasians (22). There has been some association observed in blacks between sweat gland activity and conductance (36), which may be because of the chemical composition of sweat (5). The increased electrical resistance observed in blacks implies increased cohesion or thickness of stratum corneum (32).

Human skin is individually variable, so interpretation of studies done on separate populations (often with different methods), are difficult to interpret (5). Parallel studies are particularly needed in order to define genuine racial differences (5). A summary of racial differences between black and Caucasian skin is seen in Table 3.

Age

Studies on age differences in skin sensitivity are rare and not collectively conclusive (16). No differences in potential irritancy have been observed in subjects between 18 and 50 years of age (17); although the skin of younger adults was demonstrated to be more sensitive than that of elderly subjects (16). Interestingly, however, whereas tactile sensitivity has been shown to decrease with age (22), pain sensation is preserved (22). Studies in elderly subjects have demonstrated both decreased sensory nerve function and decreased skin innervation (22). The potential for visible irritation also decreased with advancing age (16). Although less reaction to an irritant stimulus was observed in elderly subjects, aged subjects took longer to heal (17).

Assessment of barrier function in the elderly compared with younger adults demonstrated a decreased difference in TEWL measurements after SLS exposure in the elderly (16). Although the thickness (16) and number of layers in the stratum corneum (16) do not change, turnover time in the elderly did increase (16). Elderly patients were also shown to have decreased sweat function (37), capability of inflammation and repair, skin hydration and peripheral microcirculation (37).

Although the number of personal care products aimed specifically at children continues to expand, reports in the medical literature on skin sensitivity in children is almost non-existent. Children, however, have a higher surface area-to-body mass ratio, and therefore receive higher systemic exposure from dermal use of products (38).

Anatomical site

Assessment of neurosensory and physiological differences in skin at different anatomical sites has been performed using sensory stimulators, irritants and various methodologies, which evaluated structural components of the epidermis. Differences in skin sensitivity between anatomical regions have been observed.

Exposed skin

The nasolabial fold has been reported to be the most sensitive region (39) of the facial area, followed by the malar eminence (39), chin, forehead and upper lip (39). Conflicting evidence with regard to sensitivity has been reported with regard to arms, legs and torso (16). SLS sensitivity testing found that sensitivity increased from the wrist to the cubital fossa area (17).

Analysis of structural differences found that stratum corneum density varies tremendously by anatomical site: palms and soles are the thickest, whereas the genital area is the thinnest (40). The rate of turnover in the stratum corneum (36), 10 days in facial areas, is longer elsewhere (40). Stratum corneum thickness yielded inconsistent results (34). TEWL following SLS exposure was found to be greater at the wrist than other sites on forearm (17).

Vulva

The vulva differs substantively from exposed skin in numerous characteristics likely to affect vulvar susceptibility to topically applied agents; a summary is presented in Table 4(14). The outer mons pubis and labia majora are keratinized and stratified, much like skin in other areas (41). The vulva, however, is also characterized by a frictional component, occlusion, increased hydration (41), increased hair follicles and sweat glands and increased blood flow (14). The labia minor (inner third) through the vestibule, which is increasingly hydrated, is thinner, not keratinized or clearly stratified and absent of hair follicles or sweat glands (14).

Safety-testing protocols are typically designed to be done on exposed or partially occluded skin (14) and routine testing of potential irritants on the vulva itself are not logistically feasible (14). The elevated hydration of the vulvar area makes measurements difficult (29). Developed methods are, in general, less suitable to the vulvar area and observed changes less dramatic (28).

Permeability testing done in keratinized vulvar skin, indicates that it may be more permeable than other keratinized skin (41), although

Table 3. Racial differences in skin properties – a comparison between the black and Caucasian races

Skin property	Comparison results	References
Stratum corneum thickness	Equal in blacks and Caucasians	Freeman et al. (1962) (49) Thomson (1955) (57)
Number of cell layers in stratum corneum	Higher in blacks	Weigand et al. (1974) (58)
Stratum corneum resistance to stripping	Higher in blacks	Weigand et al. (1974) (58)
Lipid content in stratum corneum	Higher in blacks	Reinertson and Wheatley (1959) (53)
Electrical resistance of stratum corneum	Higher in blacks (twofold)	Johnson and Corah (1963) (50)
Desquamation of stratum corneum	Higher in blacks (twofold)	Corcuff et al. (1991) (51)
Corneocyte size	Equal	Corcuff et al. (1991) (51)
Amount of ceramides in stratum corneum	Lower in blacks	Sugino et al. (1993) (59)
Variability of structural parameters of stratum corneum	Increased in blacks	Weigand et al. (1974) (58)
Spectral remittance	Lower in blacks (above 300 nm – two to threefold)	Anderson and Parrish (1981) (60)
UV protection factor of epidermis	Higher in blacks (three to fourfold – 13.4 versus 3.4)	Kaidbey et al. (1979) (61)
UV protection factor of stratum corneum	Higher in blacks (3.3 versus 2.1)	Kaidbey et al. (1979) (61)
UVB transmission through epidermis	Lower in blacks (fourfold, 7.4 versus 29.4)	Kaidbey et al. (1979) (61)
Stratum corneum UVB transmission	Lower in blacks (30. versus 47.6)	Kaidbey et al. (1979) (61)
<i>In vitro</i> penetration of fluocinolone acetonide	Lower in blacks	Berardesca and Maibach (1996) (32)
<i>In vitro</i> penetration of water	No difference	Berardesca and Maibach (1996) (32)
	Differences	Bronaugh et al. (1986) (62)
Topical application of anaesthetic mixture	Less efficacy in blacks	Hymes and Spraker (1986) (63)
<i>In vivo</i> penetration of C-labelled dipyrithione	Lower in blacks (34% lower)	Wedig and Maibach (1981) (64)
<i>In vivo</i> penetration of cosmetic vehicle	Lower in blacks	Wedig and Maibach (1981) (64)
Methylnicotinate-induced vasodilation	Time to peak response equal	Guy et al. (1985) (65)
	Slower in blacks	Kompaore et al. (1993) (26) Berardesca and Maibach (1990) (66)
Baseline TEWL	Higher in blacks	Kompaore et al. (1993) (26)
	Higher in blacks (<i>in vitro</i>)	Wilson et al. (1988) (67)
Reactivity to SLS (measured by TEWL)	Higher in blacks	Wilson et al. (1988) (67)
Reactivity to dichlorethylsulphide (1%)	Lower in blacks (measured by erythema, 15% versus 58%)	Marshall et al. (1919) (68)
Reactivity to <i>o</i> -chlorobenaylidene malonitrile	Lower, longer time to response in blacks	Weigand and Mershon (1970) (69)
Reactivity to dinitrochlorobenzene	Lower in blacks, but trend toward equalization after removal of stratum corneum	Weigand and Gaylor (1974) (70)
Stinging response	Lower in blacks	Frosch and Kligman (1981) (71)
	Equal	Grove et al. (1984) (72)

SLS = sodium lauryl sulphate; TEWL = transepidermal water loss; UV = ultraviolet; UVB = ultraviolet B.

evidence is somewhat conflicting (14). The discrepancy may be related to the specific chemical tested and its postulated mechanism of tissue penetration. Polar molecules, surfactants and steroids, known to have different polarities and therefore different penetration characteristics, have demonstrated sensitivity differences predicted by their chemical structures (14).

Non-keratinized vulvar skin exhibits clearly increased permeability (14) related to the absence of keratin and loosely packed, less structured

lipid barrier (14). In addition, the inner epithelia are thinner, representing a shorter distance to penetrate (14). Buccal tissue is often employed in a surrogate model for vulvar testing (14), as it has very similar structure and biochemistry (14). Buccal skin has been demonstrated to be 10 times more permeable than keratinized skin (41).

An association between facial skin reddening as a result of topical product use and the likelihood of vulvar erythema was shown in a recent

Table 4. Differences between keratinized vulvar skin and other regions of the body

Characteristic	Difference in vulvar skin	Reference
Occlusion	Increased	Farage and Maibach (2004) (14)
Permeability	Increased	Lesch et al. (1989) (73) van der Bijl et al. (1997) (74)
Friction	Increased	Elsner et al. (1990) (75)
Heterogeneity	Markedly increased	Elsner et al. (1990) (75)
Hydration	Increased	Elsner et al. (1990) (75) Erickson and Montagna (1972) (76)
Number of hair follicles	Increased	Elsner et al. (1990) (75) Britz and Maibach (1985) (77) Elsner and Maibach (1990) (78)
Number of sweat glands	Increased	Elsner et al. (1990) (75) Elsner and Maibach (1990) (78)
Blood flow	Increased	Elsner et al. (1990) (75)
Innervation	Increased	Elsner et al. (1990) (79)
Capacitance	Increased	Marren et al. (1992) (44)
Baseline TEWL	Increased	Marren et al. (1992) (44)
Hydrocortisone absorption	Increased ^a	Britz et al. (1980) (48) Elsner and Maibach (1991) (27)
Reactivity to BKC	Increased ^a	Britz and Maibach (1979) (80)
Reactivity to maleic acid	Increased ^a	Britz and Maibach (1979) (80)
Reactivity to SLS (low concentration)	Decreased	Elsner et al. (1991) (81)

^aCompared specifically to forearm.

BKC = benzalkonium chloride; SLS = sodium lauryl sulphate; TEWL = transepidermal water loss.

study. The results of this study showed that individuals who presented with vulvar erythema at study enrolment reported statistically higher frequency of observable facial skin reddening with use of topical products (42).

Although the vulvar area may be particularly susceptible to cutaneous irritation (43), little objective published data exists on the relationship between feminine hygiene products and sensitive skin (11). Irritant reactions to feminine care products have been reported (44) with a few feminine products that contain chemicals known to be irritants in certain doses (20, 44). However, the potential for heightened vulvar susceptibility to topical agents is not widely reported in literature (14). The contribution to irritation by topical agents, though, is substantial (14, 41) and often underestimated (41). In fact, 29% of patients with chronic vulvar irritation were demonstrated to have contact hypersensitivity, and 94% of those were determined to have developed secondary sensitization to topical medications (44). Thus, reported sensitivity in the vulvar area, may often be related to underlying contact hypersensitivity because of excessive use of topical hygienic and medicinal preparations (45).

Available bioengineering techniques are in general less suited for quantification of irritation in the vulvar area (28). TEWL, capacitance and pH, all invisible skin surface changes, are less sensitive in the well-hydrated environment of the vulva (28). Methods measuring inflammatory reactions are more sensitive, in general than those measur-

ing other sensitivity parameters (28), and are better used in combination than alone. The authors suggest that blood flow, pH and colour reflectance, used in combination, were found to be the best approach to measuring sensitivity to irritation in the vulvar area, with increased sensitivity and specificity compared with any individual assessment (28).

Safety testing must consider the potential for heightened permeability of skin in the vulvar area and increased secondary sensitization (14). Modification of risk assessment is also required, possibly by the insertion of uncertainty factors into the quantitative risk assessment (QRA) system of risk calculation (14). Factors in range of 1–10 for keratinized vulvar skin and 1–20 for mucosal tissues, based on permeability, have been proposed (14).

Cultural factors

The first question that must be asked is whether a subgroup of people who have broad reactivity to personal care products genuinely exists. It has been proposed in both the popular media (46) and the medical literature (10) that the increasing incidence of sensitivity represents a 'princess and the pea' effect, wherein it has become culturally fashionable to claim sensitive skin. A reported prevalence of greater than 50% in women on two separate continents (2, 3) defies its perception as a minority complaint and tends to support a psychosocial component. The phenomenon is

recorded in all industrial nations (2), however, and the prevalence reported in women from two continents was virtually identical ((52%) (2) and 51.5% (3)), lending credibility to consumer complaints supported by the observation that avoidance of products containing potential irritants can eliminate hypersensitivity (18).

Cultural factors may play a role too. Hygiene practices are the most common cause of vulvar irritation (41). Fastidious cleansing routines (with douches, perfumes, medication, antifungal medications and contraceptives), which often precede irritation (41) undoubtedly have some cultural component.

Environmental factors

A majority of sensitive skin sufferers report unpleasant sensory responses to cold temperatures, wind, sun, pollution and heat (2, 7). An increased susceptibility to SLS was observed in the winter compared with the summer (17); it is known that low temperatures and humidity characteristic of winter cause lower water content in the stratum corneum (17).

Other host factors

Numerous other host factors, which could influence skin include unusual occupational or leisure exposures to chemicals (10) and home climate control measures (10). Long-term or excessive use (7) of personal care products can also create sensitivities. Daily topical use of corticosteroids has been demonstrated to produce fragile skin (7), and excessive use of topical medications has been demonstrated to be the source of up to 29% of vulvar dermatitis. Drug-induced sensitivity is also possible, although no reports on that issue were uncovered. Interestingly, the thickness of the epidermis, in one study, was demonstrated to be inversely proportional to the number of years that the subject had smoked, with a $P = 0.0001$ (34).

Another important consideration is the relationship of sensitive skin to other dermatological conditions. Atopic dermatitis (AD) is considered by many to be a possible predisposing condition (3, 7). A positive relationship has been demonstrated between AD and stinging (7) and the density of cutaneous nerves has been demonstrated to be higher in atopic skin than in normal skin (47). Also, baseline TEWL in uninvolved skin in AD patients, which is higher than that of normal subjects (31), was shown to predict susceptibility to irritants in other sites (31). Atopy in general has been linked by some

authors to the phenomenon of sensitive skin (31). Patients with respiratory atopy and active rhinoconjunctivitis were demonstrated to have increased skin susceptibility to irritants (30). It has been conjectured that alloallergens may disrupt barrier function, thereby increasing skin susceptibility (30). An association between sensitive skin and rosacea has also been postulated. In one study of rosacea patients, 64% were found to be also stinger positive (47). Pulsed dye laser treatment of rosacea was demonstrated to result in decreased stinging (47).

Discussion

The goal of premarket safety testing is to avoid unexpected consumer effects to marketed products (20). Skin testing is typically conducted tier-wise with increasing robustness (14); such testing combined with judicious product formulation lends confidence to market release (14). Recently, however, we have seen that safety-testing methods may not be robust enough (13). Consumers discriminated between products based on how they felt during use (13), basing product preferences on perceived effects not predicted by premarket testing (13).

Methods are needed which are capable of detecting very subtle skin benefits or potential for adverse effects. Testing has been done primarily on normal subjects, bringing into question the need to focus on examining populations that may be inherently more sensitive to irritant effects (14). Limited studies, which enrolled only subjects shown to have sensitive skin did find better correlation (11).

Few studies have been performed in parallel and fewer still with a multiple-irritant panel. Effective testing will require multiple regimes to identify truly sensitive people (1). A sensitive skin panel must be approached with great caution (8) however, and must define relevant exposures, limit confounding factors, and include irritants of different mechanisms. Correlation between sensory and objective data may be associated primarily with higher levels of exposure (4). In addition, current differences reported in SLS response may be related to the fact that two different forms of different irritant potentials have been employed (17).

At present, associations between observed reactivities are weak (10) and underlying pathophysiological factors poorly understood (18). Although it is clear that specific individuals clearly have heightened sensitivity to different kinds of sensory and physical irritants, observed reactions are not predictive of generalized

sensitivity, and the relationship between observed sensitivities is cloudy (8, 18). Recent evidence suggests that sensitive skin may not be a single condition, but one that encompasses different categories of subjects and sensitivities based on different mechanisms (9).

Sensory differences may be related to innervation (39). Dermal nerve fibres extend throughout viable epidermis as free nerve endings (39), but the epidermal component of this network is still poorly characterized (39). Epidermal nerve density variation could explain the different sensitivity thresholds in various anatomical sites (22). Although no differences in innervation have yet been observed (39), little research on this mechanism has been performed.

Barrier function has been shown to be a critical component of skin discomfort (11, 18). The permeability barrier in the stratum corneum requires the presence of well-organized intracellular lipids (7, 18), and depends highly on lipid composition (16). Increased neutral lipids and decreased sphingolipids are associated with superior barrier properties (16). Irritation results from the abnormal penetration in skin of potentially irritating substances and a resulting decrease in the skin tolerance threshold (7). A weak barrier inadequately protects nerve ending and facilitates access to antigen presenting cells, a mechanism, which would support an association with atopic conditions (18).

The lipid content of the stratum corneum has been shown to be a more accurate predictor of skin permeability than stratum corneum thickness or cell number (16). Alterations of baseline capacitance values imply barrier impairment and support the view that hyperreactivity to water-soluble irritants results from increased absorption (9).

Subclinical irritation may be the key to understanding sensitive skin (4). Sensations elicited by treatment with different products are generally discerned before observable differences (4). Visual irritation tests by definition measure lasting effects, whereas sensory effects are immediate (15). There is also indication that the skin has been damaged histologically before visible signs of inflammation or skin dryness. TEWL levels have been shown to increase without objective irritation (4), as has the release of inflammatory mediators (4, 36). These findings have led to the hypothesis that clinical signs occur only when the threshold level of irritation is exceeded (4).

Conclusion and Recommendations

Global marketing seeks to provide safe and useful products to an audience with tremendous potential differences in race, age, sex, skin type,

culture, habits and practical use of marketed product (5). It has become evident recently that sensory effects not predicted by current premarket testing are the main purchasing criteria of the consumer. An objective for improved testing would be the identification of a sensitive skin panel in which subjective data consistently correlated with objective data (1), and which includes irritants of different mechanisms and receptor types (1). Larger study populations are needed in order to overcome individual variability to obtain reproducible results (14). Tools to further exaggerate exposures, enhance ability to clinical score irritation (visual or via instrumentation), and identify new objective endpoints for subjective sensory effects are also needed (13). The challenge of the future is to clarify the still murky correlation between self-perceived consumer sensory irritation and objective indications of clinical irritation, a correlation, which is to date absent from the published literature (1).

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Address:
Miranda A. Farage, PhD
The Procter and Gamble Company
Winton Hill Business Center
6110 Center Hill Road, Box 136
Cincinnati
OH 45224
USA
Tel: +1 513 634 5594
Fax: +1 513 634 7364
e-mail: farage.m@pg.com