

The complex problem of sensitive skin

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There exists within the population subsets of individuals who display heightened skin reactivity to materials the majority find tolerable. In a series of investigations, we have examined interrelationships between many of the endpoints associated with the term 'sensitive skin'. In the most recent work, 58 volunteers were treated with 10% lactic acid, 50% ethanol, 0.5% menthol and 1.0% capsaicin on the nasolabial fold, unoccluded, with sensory reactions recorded at 2.5 min, 5 min and 8 min after application. Urticant susceptibility was evaluated with 1 M benzoic acid and 125 mM *trans*-cinnamic acid applied to the volar forearm for 20 min. A 2 × 23-h patch test was also conducted using 0.1% and 0.3% sodium dodecyl sulfate, 0.3% and 0.6% cocamidopropyl betaine and 0.1% and 0.2% benzalkonium chloride to determine irritant susceptibility. As found in previous studies, increased susceptibility to one endpoint was not predictive of sensitivity to another. In our experience, nasolabial stinging was a poor predictor of general skin sensitivity. Nevertheless, it may be possible to identify in the normal population individuals who, coincidentally, are more generally sensitive to a range of non-immunologic adverse skin reactions. Whether such individuals are those who experience problems with skin care products remains to be addressed.

Key words: contact urticaria; irritant contact dermatitis; safety assessment; sensitive skin; sensory effects. © Blackwell Munksgaard, 2005.

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It is widely reported that there is a proportion of the population who have, or believe themselves to have 'sensitive skin', that is they have a reduced tolerance to frequent or prolonged use of cosmetics and toiletries. In a recent publication (1), approximately 50% of women and 40% of men surveyed regarded themselves as having sensitive skin. Some suggest that the perception of 'sensitive skin' is possibly influenced by the media, as some published data show no correlation between objective skin findings and complaints about sensitive skin (2). Yet, there are findings to suggest that sensitive skin is a real issue (3). However, the concept of 'sensitive skin' remains an elusive, complex issue for dermatologists and industry alike, which makes it difficult to investigate.

There is huge variability in the presentation of sensitive skin, and the symptoms reported can include subjective effects such as stinging, itching and burning or visual irritation such as erythema, desquamation, papules and wheals, following the use of a cosmetic or a personal care product (1–4). These effects may be a result of allergic or irritant contact dermatitis, urticaria, eczema, psoriasis, etc. This wide variability in symptoms

and reactivity presents difficulties when attempting to establish a simple yet robust testing regime for selecting a sensitive skin panel, which can be used to investigate specific irritant phenomena or assessing the irritancy of new or existing home and personal care products. There is a variety of test methods, which may be used to investigate different irritant endpoints (5–8); however, it would be convenient to have one test criterion which could be utilized to identify a sensitive person; some have suggested the Sting test (5) could be suitable, but we question how realistic this is. Therefore, in the present study, we chose to investigate the interrelationships between certain of the endpoints associated with sensitive skin, including sensory irritation, urticaria and irritant contact dermatitis to different surfactants. The aim of this work being to determine whether there is any relationship between sensitivity to one stimulus and sensitivity to another.

Materials and Methods

Study population

58 healthy Caucasian adults, 19 males and 39 females, aged 22–58 years (mean age: 39 years)

were enrolled onto the study after providing written informed consent. The volunteers were recruited from Unilever staff at the laboratory site. Records of panellists' participation in previous studies were examined, and all panellists who demonstrated consistent strong responses to either lactic acid or sodium dodecyl sulfate (SDS) (approximately 16%) were approached to take part in the study. Of these, approximately 60% were able to participate. Panellists with a current skin condition (including eczema, dermatitis and psoriasis) were excluded from the study.

Materials

Sensory perception test. 10% active ingredient (ai) (w/v) lactic acid was prepared in ultrapure water from an 85% racemic D-L syrup. 0.1% (w/v) capsaicin was prepared from minimum 95% capsaicin in mineral oil. 50% (w/v) ethanol was prepared in ultrapure water. 0.5% (w/v) menthol was prepared in ultrapure water. All of these chemicals were obtained from Sigma Chemical, Poole, Dorset.

Covered patch test. 0.1% and 0.3% (w/v) SDS obtained from Sigma Chemical were prepared in ultrapure water. 0.3% and 0.6% (w/v) cocamidopropyl betaine (CAPB), obtained from Goldschmidt UK Ltd, Milton Keynes, Buckinghamshire, was prepared in ultrapure water. 0.1% and 0.2% (w/v) benzalkonium chloride (BKC), obtained from Sigma Chemical was prepared in ultrapure water.

Volar forearm test. 1 M benzoic acid was prepared in petrolatum 125 mM *trans*-cinnamic acid was prepared in pet. Both chemicals were obtained from Sigma Chemical.

Methods

Sensory perception test. 10% (w/v) lactic acid was rubbed briskly over one nasolabial fold of each panellist, ultrapure water was rubbed over the contralateral nasolabial fold. The panellists were asked to complete a questionnaire during treatment at 0, 2.5, 5 and 8 min after treatment, detailing the type and intensity of any sensory effect experienced utilizing a 4-point scale (none = 0, slight = 1, moderate = 2 and severe = 3). The level of stinging elicited by the application of 10% (w/v) lactic acid on the nasolabial fold at each time was given a numerical value as detailed. If the sum of the responses at these time points was ≥ 3 , the panellist was classified as a stinger; if the sum of the values was < 3 , the panellist was classified as a non-stinger. Time 0 was not included in the calculation, as the initial contact of the test substance with the skin can

result in a false sensory response such as a temporary cooling of the skin.

The same procedure was carried out in subsequent weeks using 50% (w/v) ethanol, 0.5% (w/v) menthol and 0.1% (w/v) capsaicin. Capsaicin was dissolved in mineral oil; hence, for this material only, mineral oil was tested on the contralateral side of the nose, in place of ultrapure water. Only one material was tested on any given day, and several days were left between testing to reduce the possibility of cumulative effects.

Visual skin parameters (i.e. erythema and dryness) at each of the test sites were assessed prior to treatment, immediately after and 24 h after treatment, for panellists care, to ensure that no adverse or prolonged reactions developed. At each application panellists were given a list of descriptors, which had been adapted from previous publications (9, 10), to aid them in defining the sensation they were experiencing. The terms were defined as follows, itch as the desire to scratch, burning as a painful sensation that follows a thermal burn, stinging as a sensation that occurs when alcohol is applied to a cut or abrasion, tingle as a lively 'pins and needles' sensation and prickle as a sensation caused by the movement of rough fabrics over the skin.

Volar forearm test. Two different urticants were chosen for testing on the volar forearm, 50 μ l of 1 M benzoic acid and 125 mM *trans*-cinnamic acid. The materials were applied to the volar forearm via a 12-mm Finn chamber on Fixomull tape (manufactured by BDF Beiersdorf AG Hamburg, Germany) for a period of 20 min. Panellists had one material applied to each volar forearm. During the 20 min treatment period, panellists were asked to complete a question-naire regarding any sensory effects they may have experienced during the application period. Visual skin parameters (i.e. erythema and dryness) were assessed prior to treatment, 10 min, 1 h, 2 h and 4 h after removal of the materials, and a recovery assessment was conducted 24 h later. Wheal and/or flare reactions were recorded by measuring the largest diameter of the reaction.

Covered patch test. 50 μ l of the test materials were applied to patches consisting of 4 $\times$ 12-mm Finn chambers on Fixomull tape (manufactured by BDF Beiersdorf AG Hamburg, Germany). Materials were applied according to predetermined randomized treatment site plans. Each panellist had two patches applied, one on each upper outer arm. Both patches contained the same test materials, however, one patch contained lower concentrations than the other and also held the negative control, ultrapure water. On the patch holding the higher concentrations, one site remained blank.

The patches were applied for 23 h, after which they were removed, the treatment sites wiped, marked and visual skin parameters assessed 1 h later. The second patches were then applied to the same sites for a further period of 23 h. Visual skin parameters were assessed 1 h and 25 h after the second patches were removed. Any comments made by panellists regarding sensory effects were also recorded.

For each of the above three different test procedures, if a test material caused an unacceptably high level of irritation, then that material was removed and no subsequent exposure to that concentration of test material was made at that treatment site. However, to ensure all panellists completed all three test procedures, the panellist was asked to continue with the remaining test procedures within the allotted time frame.

Visual assessment of reactions

Erythema, dryness and other visual parameters were assessed by trained skin assessors using an open ended grading scheme as previously published (11).

Analysis of data

Statistical analysis was performed by Data Sciences, Unilever Colworth. Binomial probability was conducted to establish whether being sensitive to one stimulus had any bearing on being sensitive to another stimuli. A χ^2 test was performed to compare the results obtained with those which would be expected if the test methods/materials were independent of each other.

Results

Sensory perception test

The sensory score for all panellists for each material was calculated; a sensory score of 3 or more was considered a significant response. 26 panellists experienced a significant response to 10% (w/v) lactic acid, 7–50% (w/v) ethanol, 22–0.1% (w/v) menthol and 48–0.1% (w/v) capsaicin. Figure 1 indicates the number of panellists recording a significant response to 0, 1, 2, 3 or all 4 of the sensory irritants tested. Only 4 of the panellists recorded a significant sensory response to all 4 of the materials tested. Thus, a response to one sensory irritant did not mean that a panellist would also experience sensory irritation to the other chemicals tested.

As previously reported by Green and Bluth (9), the chemosensory irritation produced by the 4 chemicals was not unidimensional. The total

number and type of the predominant comment and 'other' comments made at 2.5, 5 and 8 min for all panellists were calculated. Table 1 shows the type and percentage of the sensory comments made to the 4 materials. 10% (w/v) lactic acid elicited mainly itching and stinging, 50% (w/v) ethanol elicited itching, stinging and burning, 0.5% (w/v) menthol elicited stinging and cooling and 0.1% (w/v) capsaicin elicited stinging and burning.

On the basis of responses to the aforementioned specific sensations alone, fewer panellists were classified as sensitive than if all sensory reactions to each material were taken into account (using the criteria of sum total ≥ 3 to define 'sensitive' individuals). For example, following treatment with 0.1% (w/v) capsaicin, of the 58 panellists, 48 were classified as being sensitive, regardless of the sensations recorded, but after screening for a burning sensation only 30 were considered sensitive. 10% (w/v) lactic acid produced 26 sensitive panellists, but only 13 of these were identified as 'stingers' after screening out other sensory comments. 22 panellists were categorized as being sensitive to 0.5% (w/v) menthol regardless of the sensation, but after screening for cooling sensations, only 9 were still classified as sensitive.

Covered patch test

There was a high level of response to the different surfactants tested. The number of panellists who developed an erythema grade of ≥ 6 by the 48-h assessment was calculated for each material tested, Table 2. There were also 7 panellists who also developed an erythema grade of ≥ 6 to ultra-pure water by the 48-h assessment.

A dose – response relationship was observed for SDS with 32 panellists developing an erythema grade of ≥ 6 –0.1% (w/v) and 50–0.3% (w/v). Neither CAPB or BKC elicited a clear dose –

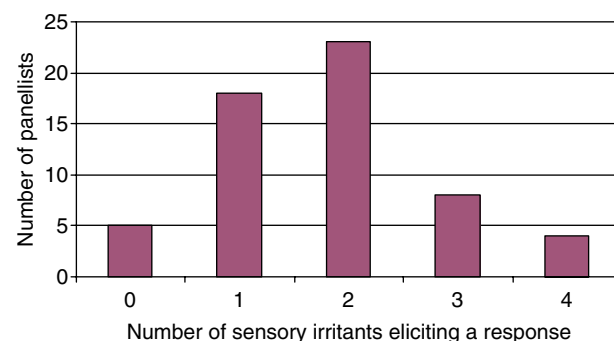


Fig. 1. Number of panellists experiencing a sensory response.

Table 1. Sensory perception test – distribution of sensory comments reported to each sensory irritant

Test material (%)	Itch		Sting		Burn		Cooling		Prickle		Tingle		Total number of comments
	Co	%	Co	%	Co	%	Co	%	Co	%	Co	%	
10 lactic acid	39	35.5	47	42.7	10	9.0	1	0.9	2	1.8	11	0.1	110
50 ethanol	10	20.8	12	25	13	27.1	1	2.1	3	6.3	9	18.6	48
0.5 menthol	16	14.5	26	23.6	17	15.5	28	25.5	5	4.5	18	16.4	110
0.1 capsaicin	12	7.2	58	34.9	78	47.0	0	0.0	2	1.2	16	9.7	166

Co = number of comments recorded; % = percentage of total comments recorded.

response relationship. CAPB elicited a lower level of irritation than either SDS or BKC, with approximately half the number of panellists developing an erythema grade of ≥ 6 more to the highest concentration of CAPB compared with the number developing an erythema grade ≥ 6 to either the highest concentration of SDS or BKC.

Reactivity to one surfactant did not necessarily predict a response to one of the other surfactants, and only 12 individuals developed an erythema grade of ≥ 6 to all the surfactants at both concentrations.

Volar forearm test

39 panellists developed an erythema grade of ≥ 6 –1 M benzoic acid, and 11 panellists developed an erythema grade of ≥ 6 –125 mM *trans*-cinnamic acid. Three of the panellists who elicited strong responses to 125 mM *trans*-cinnamic acid did not develop a high response to 1 M benzoic acid.

Reactivity to multiple tests

The panellists who developed the highest responses in each test were identified, and these ‘top reactors’ for each test were compared to determine whether a strong response in one test method was indicative of a high response in the other test methods.

Only one panellist of the 58 tested developed a strong response to all of the irritants in each test method, and 1 panellist had a strong response to all but 125 mM *trans*-cinnamic acid.

Of the 11 people who developed the strongest responses to 1 M benzoic acid and 125 mM *trans*-cinnamic acid, 7 were also determined as top reactors to the surfactants tested in the covered patch test.

Of the 4 panellists who developed a strong response to all 4 of the sensory irritants, 1 also reacted strongly to both of the urticants (benzoic acid and *trans*-cinnamic acid), 1 reacted strongly to just 1 M benzoic acid and the other two did not respond to either.

Independence of tests

To establish whether the test methods were independent of each other, binomial probability analysis was performed. To obtain the *P*-value, the probability ‘*z*’, that any given panellist responded to all seven tests (defined as the covered patch test, 1 M benzoic acid, 125 mM *trans*-cinnamic acid, 10% (w/v) lactic acid, 0.1% (w/v) capsaicin, 0.5% (w/v) menthol and 50% (w/v) ethanol), assuming them to be independent, was calculated. The values shown are the proportion of panellists who were classified as ‘most sensitive’ to the tests in the order described:

$$z = \frac{23 \times 21 \times 17 \times 19 \times 18 \times 15 \times 15}{58}$$

z is thus the probability that any one person is classified as responding to all seven tests (assuming the tests to be independent). One

Table 2. Covered patch test – number of panellists developing an erythema grade of 6 or more by the 48-h assessment

Test material	Number of panellists' erythema (grade <6)	Number of panellists' erythema (grade ≥ 6)
0.1% SDS	25	32
0.3% SDS	7	50
0.3% CAPB	35	22
0.6% CAPB	36	21
0.1% BKC	18	39
0.2% BKC	14	43
Ultrapure water	50	7

1 panellist was absent at the 48-h assessment, therefore their data are not included for this test.

panellist was in the sensitive group for all seven tests thus:

$$P = 1 - (1 - z)^{58} = 0.01646$$

This approximately represents the probability of at least one panellist of the panel of 58 being classified as 'sensitive' to each test simultaneously by chance alone, assuming the tests to be independent. Because the *P*-value was <0.05 and hence significance was taken at a 5% level, the results of the analysis suggested that the tests were not independent.

A χ^2 -test was carried out to compare the data obtained against the data expected, given the assumption that all the test methods and materials used were independent of each other. In order to do this, the number of tests each panellist was sensitive to was calculated. These results were collated to find out how many panellists were sensitive to 0, 1, 2 to 7 tests. These results formed the basis of the 'observed results' for the purposes of the χ^2 -test. These were compared with the 'expected results' in each category, obtained by intensive simulation. Table 3 shows the observed and expected values for each category.

A *P*-value of 0.0937, which is significant at a 10% level, was obtained. This indicated that there is weak evidence to suggest that the proportion of individuals falling in each category in the table differs from what might be expected, were the tests random and independent.

This result was supported further by the observation that the nature of the differences between observed and expected counts, in that a larger-than-anticipated proportion of panellists fell in both the lowest (least sensitive) and the highest (most sensitive) categories. Therefore, the suggestion that a sensitive panel could be identified was supported by this result.

Discussion

Sensitive skin is generally defined as a function of a reduced tolerance to frequent or prolonged use of cosmetics and toiletries (12). This intolerance can manifest itself with symptoms that range from objective signs of irritation including

erythema, dryness and scaling, to subjective irritation such as stinging and burning, etc. (3, 4). This tremendous variability in the manifestation of sensitive skin makes investigating this issue very complicated. There are a wide variety of test protocols, which are employed in an attempt to investigate sensitive skin patients and to assess the irritancy of products (4–7), many of which investigate different endpoints. It would be of value to have a single test protocol, which could be employed to identify sensitive individuals and thus assess the complete irritancy profile of a material. However, it is currently unclear whether an individual having a low threshold to one irritant stimulus is also susceptible to all other types of irritant stimuli. To address this question, it is first important to investigate the relationships between the different irritant stimuli. There has been limited work to investigate the relationship between non-immunologic skin reactions, such as stinging, urticaria and contact dermatitis from surfactants, which has reported conflicting results, suggesting that any correlations between reactivities to these types of irritant endpoints is at best weak (1–14). In the present study, we also investigated a number of different endpoints in an attempt to identify any interrelationships between them and then to determine whether there were any individuals who were broadly sensitive to all of the stimuli tested.

Panellists were recruited for this study based on their historic reactivity to lactic acid or SDS in a standard method conducted within the laboratory. Panellists who reacted strongly to either chemical were selected for participation as they were considered to be likely to be more sensitive to chemical irritants than people who developed none, or at best weak reactions to lactic acid or SDS, common positive controls used regularly within the laboratory.

The Sting test is often suggested as a suitable method for identifying people with sensitive skin (3, 5); however, there is evidence to suggest that sensitivity to lactic acid is not necessarily predictive of sensitivity to other irritants (13, 14). In the present study, four chemicals, which have been reported to induce different sensory effects (lactic acid, stinging; capsaicin, burning; menthol,

Table 3. Observed and expected values of the number of panellists sensitive to each test

	Number of test panellists were sensitive to			
	0–1	2	3	4–7
Observed (number of panellists)	22	15	9	12
Expected (number of panellists)	17.11	18.41	14.19	8.298

cooling; ethanol, a mixture of burning and stinging), were chosen to investigate various aspects of sensitivity to subjective sensory irritation. The data show that there was a great deal of variation in the reactivity to the four materials, and generally, heightened reactivity to one material was not predictive of an elevated level of response to another. Of the 58 individuals recruited on the basis of their increased sensitivity, there were 4 panellists who recorded a significant sensory response to all 4 of the materials tested, thus it would appear that a small number of individuals are sensitive to a broad range of sensory stimulants. Yet, it was not possible to predict who these individuals were from their responses to just one of these irritants, as they were not necessarily the strongest responders to each of the 4 chemicals. This finding concurs with previous work conducted by Green and Schaffer (15) who found that individuals differed greatly in their response to just 2 chemicals and endorses the view (9) that a selection of materials should be used to gauge sensitivity rather than one chemical alone. The same group has also noted that that sensory irritation arises from a variety of different receptor types, thus the use of one chemical stimulus can only provide meaningful information on irritancy to that material and possibly that of the class of chemicals to which it belongs (16). The 4 sensory irritants used in this study are all thought to act via different mechanisms (9). This evidence would suggest that when investigating the sensitivity of an individual to a sensory stimulus, it would be prudent to use more than one sensory stimulus unless a single sensory response is being investigated.

There was no relationship seen between the level of response to the two urticant materials tested. It is reported that strong reactivity to one non-immunologic urticant is not necessarily predictive of the degree of response to other such urticants (14, 17). This is further demonstrated in this study, as not all the panellists who developed a strong response to 125 mM *trans*-cinnamic acid also had a strong response to 1 M benzoic acid.

There is also some evidence to suggest that urticants produce a greater urticarial response in stingers (13). However, this view is not supported by all, as Coverly et al. (14) found little difference in the pattern of urticant reactivity between stingers and non-stingers. The results from the present study further support the view that stinging and urticaria are not closely related.

In this study, panellists were tested with 3 different types of surfactant, an anionic surfactant, SDS, an amphoteric surfactant, CAPB and a cationic surfactant, BKC. Anionic surfactants

are reported to be potent skin irritants, cationics at least equally irritating and amphoteric are reputed to be relatively non-irritating to the skin (18). As would be expected from this evidence, CAPB elicited a lower number of strong irritant responses than either BKC or SDS. Thus, it could be argued that the panellists who developed an irritant response to CAPB were more sensitive than those who did not. However, some of the individuals who developed a strong response to CAPB did not also develop a strong response to the other 2 surfactants tested. Only 12 individuals developed a strong response to all 3 surfactants at both concentrations. Thus, even when testing chemicals which elicit irritation via a similar mechanism, an irritation response to one chemical is not necessarily indicative of a response to another chemical, even one which has a similar mode of action.

It has been suggested by some that there may be a relationship between sensitivity to sensory irritants and physical irritants (5, 6, 13), however, there are others who found no relationship between the level of stinging response or reactivity to SDS (19). This study supports the latter finding, as there was little correlation between the level of response to 10% (w/v) lactic acid and the surfactants tested in the covered patch test.

It is quite clear that overall sensitivity to one stimulus is not necessarily predictive of sensitivity to another. However, this study showed a weak relationship between the different test regimes employed with both the binomial probability and χ^2 -test suggesting that there is some evidence that the different tests were not independent of each other. Thus, reactivity to one test may indicate reactivity to another test. There were also a small number of individuals tested here that were broadly sensitive to each endpoint, with one person in particular who reacted to every stimulus. This, combined with published work that suggests a relationship between reactivity to sensory irritants and physical irritants (13, 14), would indicate that there is a very small subset of individuals who will react to any stimulus applied under any test conditions. Whether these individuals are those who are more likely to react to personal care products in a normal use scenario remains to be shown.

However, it is important to note that using just one testing regime does not make it possible to identify this small subset, as the evidence indicates that there is wide variability in the reactivity of individuals, and many will, and do, react to at least one type of stimulus. Thus, when conducting investigations into skin sensitivity it would be beneficial to determine the endpoint of interest

and use the most suitable test to identify individuals who are most sensitive to that particular type of stimulus. Should it be necessary to identify a panel of individuals with more broadly sensitive skin, multiple screening tests need to be conducted.

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