

Population differences in acute skin irritation responses

Race, sex, age, sensitive skin and repeat subject comparisons

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The variability in human skin irritation responses has been well documented and can confound our ability to accurately assess differences in skin reactivity between human subpopulations. In the current analysis, results were compiled from nine acute irritation patch test studies, conducted at three test facilities over a 5-year period. Four irritant test chemicals, 20% sodium dodecyl sulphate, 100% decanol, 100% octanoic acid and 10% acetic acid, were tested in sufficient numbers of test subjects to enable the stratification of results for different human subpopulations. An increased reactivity was noted for Asian versus Caucasian subjects for each of three test chemicals, in contrast to the previously described individual study results from which these data were drawn. Male subjects were directionally or significantly more reactive to each of the test chemicals than female subjects. The oldest age cluster of subjects (56–74 years of age) was directionally or significantly less reactive than younger age clusters. There was virtually identical reactivity between self-assessed 'sensitive' and normal skin groups. Lastly, there was little correlation between the results from individual subjects tested in two or more studies with the same chemicals. These results add to our general understanding of population differences in skin reactivity and the potential implications for ingredient and product skin safety testing and risk assessment.

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Acute skin irritation responses in human test subjects can result from occluded patch test exposures to a variety of chemicals depending upon the concentration and duration of exposure. These responses can be quite variable from subject to subject (1), or within subjects (2). Therefore, populations of test subjects will tend to show a range of reactivity that can often take on the appearance of a normal distribution (3). This variability can complicate the analysis of comparative skin irritation studies, such as those attempting to discern subpopulation differences in skin reactivity. As a result, the literature on population differences in human skin reactivity tends to provide conflicting or inconsistent information (3, 4).

The human 4-h patch test was initially developed as a valid and predictive alternative to rabbit testing for the assessment of chemical skin irritation (5). Over the ensuing years, this test has been used successfully to define the chemical irritancy potential of a wide range of chemicals and

to investigate various characteristics of the skin irritation response (6). Although there is certainly inter- and intra-individual variability in subjects' irritant reactivity to different chemicals tested with this method (1, 2), experience has shown that the inclusion of approximately 30 subjects per study provides a reasonable assessment of skin irritation potential of test chemicals relative to 20% sodium dodecyl sulphate (SDS) included in each study as a positive control.

One of the 'investigative' applications of this test has been the study of racial differences in skin irritation responses. These studies have included an international interlaboratory assessment of the SDS dose-response (7), a study of test subjects distinguished by UV reactive skin type (8), and several studies directly comparing Caucasian and Asian populations (4, 9). In none of these individual studies was there a consistent finding of differences in skin reactivity among racially diverse study populations.

Other population-based differences in skin reactivity, particularly those related to sex, age and self-assessed skin 'sensitivity', have been less thoroughly investigated than racial differences, with most of the comparative evaluations based upon epidemiological patterns of response that don't clearly separate differences in reactivity from differences in patterns of exposure (3). To attempt to address these population comparisons and reassess racial comparisons, we compiled all of the data from 5 years of human 4-h patch testing specifically clustering data on common chemicals for which sufficient numbers of subjects were tested to permit subpopulation comparisons. Since the positive control irritant, 20% SDS, was tested in all studies, this provided a large number of test subjects for reactivity comparisons. Other frequently tested chemicals of varying irritancy were also included in the analysis. Comparisons were made across four different subpopulation categories: Caucasian versus Asian, male versus female, different age clusters, and subjects with self-assessed 'sensitive' skin versus those claiming normal skin reactivity. Repeat tests on certain individual subjects also allowed cross-study comparisons for response correlations.

Materials and Methods

Chemicals

Test chemicals studied included sodium dodecyl sulphate (SDS), acetic acid (HAc), 1-decanol (Dec), octanoic acid (OAc), and water. All test chemicals were obtained from a single supplier (Sigma Chemicals, St. Louis, MO, USA) and were at least 99% pure. Lack of corrosivity of the test materials (under conditions of the test protocol) was ensured prior to testing via reference to published data (9–11).

Human patch test procedure

Clinical testing was conducted between July 25, 1995 and March 9, 1999 at the California Skin Research Institute (San Diego, CA, USA), the Reed Hartman Research Center (Cincinnati, OH, USA), or Hill Top Research, Inc. (Cincinnati, OH, USA) under contract and according to protocols provided by Procter & Gamble. The procedures used were subject to review and approval by local ethical committees and all testing was conducted in accordance with the Helsinki Declaration of 1975. All procedures were described in detail to all study subjects, who individually read and signed informed consent forms. In these patch test studies, a total of 384 subjects (305 females, 79 males; ages 18–74) completed testing. Specific details of the

study populations and individual study results have been reported previously (2, 4, 9, 12, 13).

Study subjects were exposed on the upper outer arm to each test material for up to 4 h according to previously described procedures (4, 5, 9, 12–14). In each study, 20% SDS was tested as a positive control. Test materials were applied neat, or after suitable dilution, in a 0.2-mL volume to 25 mm Hill Top Chambers (Hill Top Company, Cincinnati, OH, USA). Test materials were applied to the skin sites progressively from 30 min through 1, 2, 3 and 4 h of exposure. Thus, each subject had a maximum of five patches of each test material applied, with each successive patch being applied for an increased duration of time. This incremental exposure ensured that skin reactions stronger than mild (or at most moderate) were avoided.

After each patch removal, the skin sites were gently wiped with a damp towel (to remove excess residual test material) and allowed to dry, taking care not to cross-contaminate the sites. The sites were graded at 1, 2 and 3 days after patch removal using a 4-point grading scale of increasing irritation:

0: No significant reaction.

+: Weak but unequivocal erythema over most or all of test site. The response may include some edema or other surface effects.

++: Moderate erythema that may spread beyond the edge of the treatment site. The response is usually accompanied by edema and/or surface effects (e.g. glazing, scaling) and possibly other focal injuries (hemorrhage, erosion, scabbing).

+++ : Strong, usually spreading, erythema usually accompanied by edema and possibly with injuries in depth (vesiculation, scabbing, hemorrhage).

Erythema was the primary response detected and recorded. Purely surface effects (e.g. dryness, glazing) were recorded, but were not used as determinants of positive responses. Subjects not responding to a test material after a given exposure interval were re-exposed for the next longer interval at naive skin sites (adjacent to the prior site or on the alternate arm). Once a positive response (+ or greater) occurred in a given subject, there were no further exposures of that subject to that test material.

The principles of the patch testing procedure were intended to avoid the production of strong irritation responses (6). Approximately 90% of all skin reactions were mild in severity and all skin reactions resolved quickly. A few subjects dropped out of the studies subsequent to study number assignment. All dropouts were for reasons unrelated to the procedures, and none were due to skin reactions.

Data analysis

The effective number of panelists completing the tests included all subjects who received a 4-h exposure to that test material plus any subjects for whom treatment with a given test material was stopped at an earlier exposure time due to a positive reaction. Dropouts for any reason (again, none were due to skin reactions) were not included in the data analysis. The number of subjects exposed to the different test materials is indicated in the figure legends. The data were compiled as the percent incidence of positive skin reactions to a given test material. The temporal responses were also evaluated by curve fitting (SigmaPlot for Windows, version 4.0) and TR_{50} values (the time of exposure necessary for 50% of the exposed population to show a positive skin response) were determined. Fisher exact tests were run on the collective positive versus negative patch test responses for the Asian versus Caucasian, male versus female, and sensitive versus normal skin comparisons.

To compare patch test responses across populations further, the duration of patch exposure giving a positive reaction in each test subject was 'converted' to an arbitrary severity grade as described previously (9). For example, a positive response after 0.5 h of patch exposure was assigned a maximum grade of 6 and no response after 4 h of patch exposure was assigned a minimum grade of 1. This enabled the speed of response to be factored into the population reactivity comparisons. These severity grades were then compiled for different subpopulations of interest (Caucasians, Asians, males, females, age clusters, self-assessed sensitive skin, normal skin) for each of the test materials evaluated. Subpopulation severity responses were cross-compared using Student's *t*-test. In similar fashion, repeat patch test severity grades for individual subjects were compiled for each chemical and these comparative responses were examined for correlations by linear regression analysis.

Results

Pattern and consistency of SDS response across multiple studies

The ability to make reasonable comparisons of subpopulation response patterns by combining the results of multiple patch test studies, required some confidence that the overall population response patterns were consistent from study to study. To verify this, the time response patterns to 20% SDS for each of the nine individual patch test studies were compared (Fig. 1). As shown in Fig. 1A, there was some variation in the individual time response

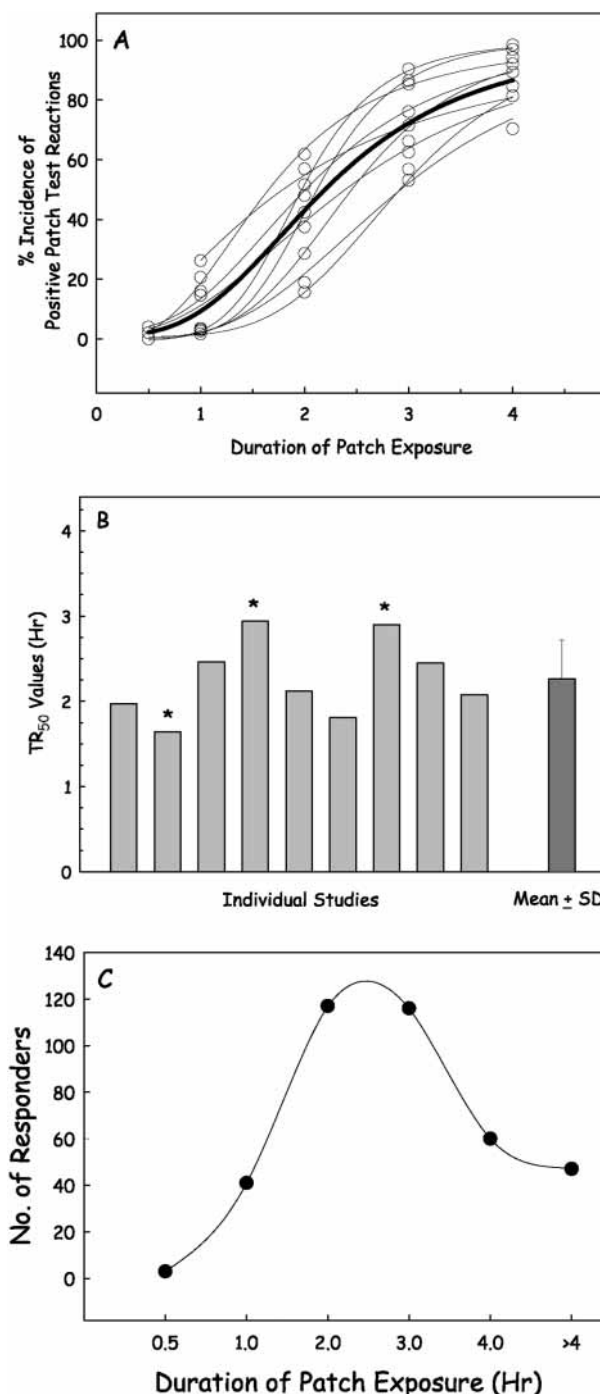


Fig. 1. (A) The patch test responses to 20% SDS, for each of nine studies, were compiled as the percent of subjects with a positive response after each duration of exposure. A 4-parameter logistic curve was fit to each data set. The bold curve shows the results for all 384 test subjects combined. (B) The individual study and combined TR_{50} values from the curves plotted in (A). Only three of the nine studies resulted in a population response pattern that was significantly different than the mean (*). (C) For all 384 test subjects, the number with positive patch test reactions after each duration of exposure.

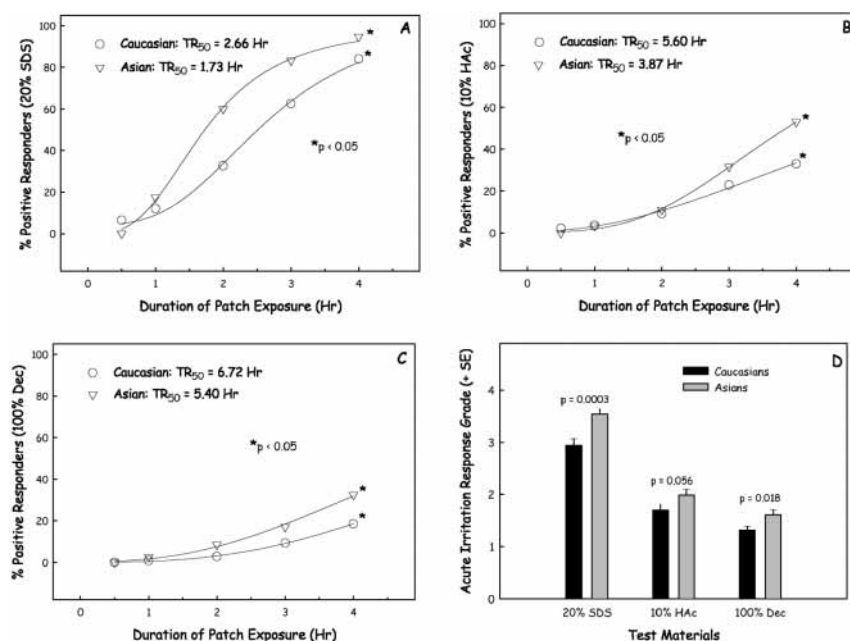


Fig. 2. (A)-(C) show the individual data and curve fits for Asian (combined Japanese and Chinese) and Caucasian test subjects patch tested with 20% SDS, 10% HAc and 100% Dec, respectively. The numbers of Asian and Caucasian subjects tested with each chemical were: SDS (115 Asian; 107 Caucasian), HAc (117 Asian; 109 Caucasian), Dec (117 Asian; 108 Caucasian). The total positive responses (by 4 h of exposure) to all three chemicals were significantly greater for the Asian subjects (Fisher's Exact Test). For (D), the time of response for each subject to each chemical was converted to an acute skin irritation response grade as described in Materials and Methods. The mean grades (+ SE) were determined and compared by statistical analysis.

patterns, most obvious at the 2- and 3-h exposure time points. However, in spite of the recognized inter- and intraindividual variability seen with human skin irritation responses (1, 2), there was a relatively consistent pattern of responses to 20% SDS at the study population level, both when compared to the composite time response curve (Fig. 1A) and when comparing the individual study and overall mean TR₅₀ values (Fig. 1B). Also, when the time of response profile was compiled for all 384 subjects exposed to 20% SDS, the pattern was a typical normal distribution (Fig. 1C).

Racial variations in skin irritation responses

Four studies conducted at one test laboratory included mixed populations of Caucasian, Chinese and Japanese subjects. Previously examined as individual studies for racial differences in skin reactivity (4, 9), the composite results from all of the studies were compiled here for the three chemicals that were included in all four studies (Fig. 2). The time response profiles for each chemical (Fig. 2A-C) showed slight but distinct reductions among the Asian (combined Chinese and Japanese) subjects in the time to respond (reduced TR₅₀ values). When the time of response values for each subject were converted to acute irritation grades (Materials and Methods), the Asian subjects had directionally or significantly increased responses to all three chemicals.

Sex variations in skin irritation responses

Though the majority of volunteer test subjects across the nine studies were female, sufficient male

subjects were tested to permit a comparison of male versus female response patterns to 20% SDS as well as the three other test chemicals (Fig. 3). With each of the four chemicals, the male subjects responded more rapidly than the female subjects, as indicated by the lower TR₅₀ values derived (Fig. 3A-D). Converting the time of response for each subject to an acute irritation grade (Material and methods), there was also a directional or significant increase in response of the male subjects to each chemical (Fig. 3E).

Age variations in skin irritation responses

Across the nine studies, the age range of the subjects was 18–74. For age comparison purposes, the subjects were grouped into the following age 'clusters': 18–25, 26–35, 36–45, 46–55, and >55. For the two stronger irritants, 20% SDS and 100% OAc, there was a significantly reduced irritation response among the oldest age cluster versus all other clusters (Figs 4A & B). With 20% SDS, this was slightly more apparent among a small subset of subjects ($n = 22$) that were 62 years of age or older (Fig. 4A). For the two weaker irritant test chemicals, 10% HAc and 100% Dec, there was a slight directional, but not a significant, reduction in response in the >55 age cluster compared to the other age groups (data not shown).

Skin irritation responses among 'self-assessed' sensitive skin versus normal skin subjects

In each of the patch test studies, subjects were asked whether they had 'sensitive skin' based on

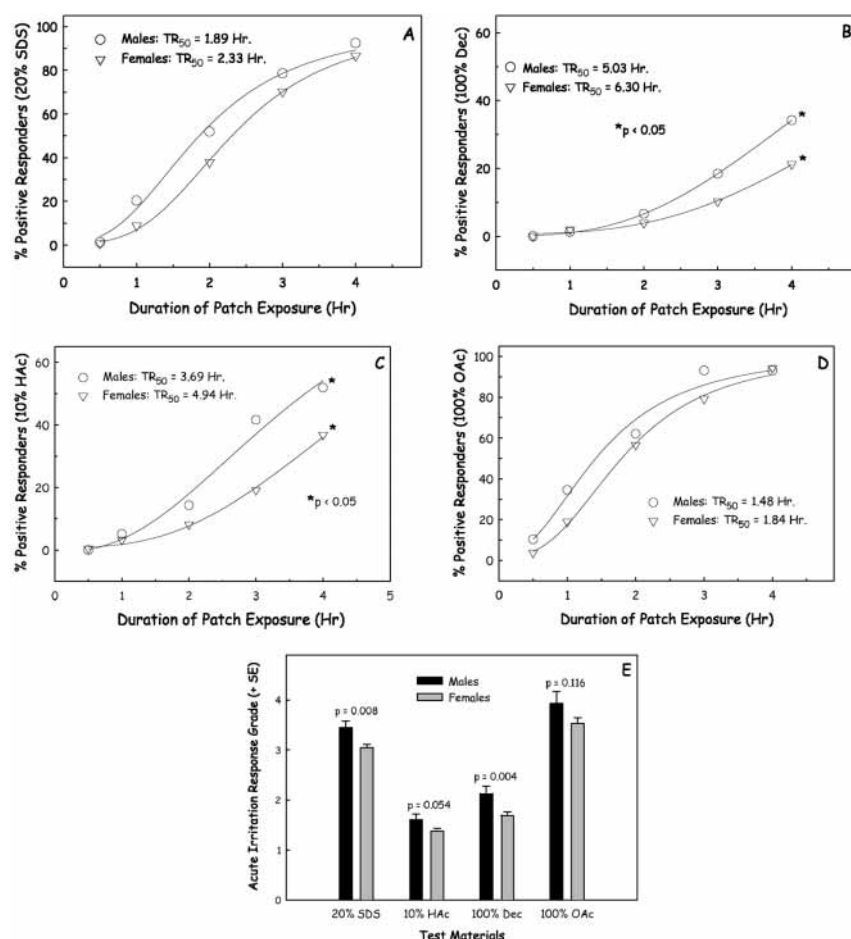


Fig. 3. (A)-(D) show the individual data and curve fits for male and female test subjects patch tested with 20% SDS, 100% Dec, 10% HAC, and 100% OAc, respectively. The numbers of male and female subjects tested with each chemical were: SDS (305 female; 79 male), Dec (203 female; 76 male), HAC (182 female; 77 male), OAc (106 female; 29 male). The total positive responses (by 4 h of exposure) to 100% Dec (B) and 10% HAC (C) were significantly greater for the male subjects (Fisher's Exact Test). For (E), the time of response for each subject to each chemical was converted to an acute skin irritation response grade as described in Material and methods. The mean grades ($\pm$ SE) were determined and compared by statistical analysis.

perceived sensitivity to skin products, clothing, susceptibility to rashes or other manifestations of clinical irritation, or even prior chemosensory testing. The patch test results for each of the four chemicals were then compared between self-assessed sensitive skin and normal skin subjects. For all four chemicals, regardless of inherent irritancy, there was no difference in the patch test reactivity between the two subject populations. Time response curves and acute irritation grades were virtually identical. The summary acute irritation grades are shown in Fig. 5. The total number of positive responders was also compared for each chemical (Fisher's Exact Test) and no significant differences were observed (data not shown).

Reproducibility of individual subject's patch test reactivity upon repeat testing

Since the nine patch test studies were conducted at three clinical testing laboratories, it was not uncommon for individual subjects to have been included in two or three different studies. For the four chemicals included in this analysis (20% SDS, 10% HAC, 100% Dec, 100% OAc) there were 56, 39, 38 and 14 repeat

test results, respectively. The acute irritation grades for each chemical were cross-compared between repeat tests to see whether a positive correlation could be observed (Fig. 6).

No correlation between the repeat test results was observed for 20% SDS, 10% HAC or 100% Dec. There was a positive correlation seen for 100% OAc. However, only 14 individuals were repeat-tested with OAc and these common subjects were retested at the same laboratory only 4 months after their original OAc patch test exposure. All of the other test materials combined the results of 38 or more subjects, from more than two studies and at test intervals of 1–3 years.

Discussion

Previous studies have underscored the difficulty in making general conclusions about racial differences in irritant skin reactivity (15) based upon individual studies in relatively small numbers of test subjects (4, 7, 9, 16–18). Our ability to identify true differences in skin reactivity based upon differences in sex, age or self-perceived skin sensitivity is also limited by the paucity of comparative studies. The

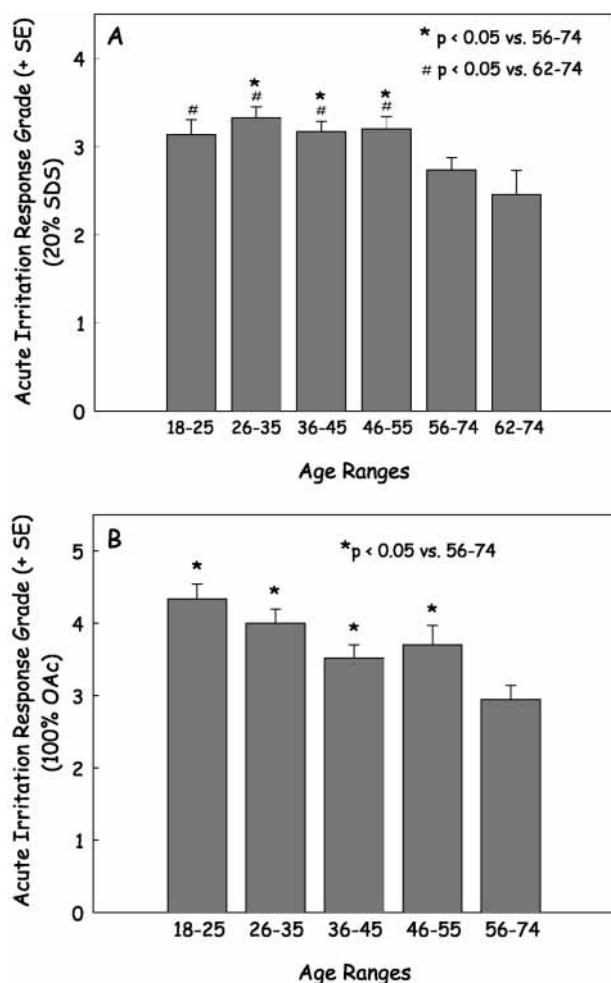


Fig. 4. A and B show the mean ($\pm$ SE) acute irritation response grades for the indicated age group clusters to 20% SDS and 100% OAc, respectively. For SDS, the numbers of test subjects in each age cluster were: 18–25 years (44); 26–35 years (77); 36–45 years (118); 46–55 years (80); 56–74 years (64); 62–74 years (22) (one subject did not have their age recorded and was omitted from the analysis). For OAc, the numbers of test subjects in each age cluster were: 18–25 (21); 26–35 (21); 36–45 (29); 46–55 (30); 56–74 (34). The mean grades for each age cluster were cross-compared by statistical analysis.

present study attempted to examine the question of differences based on race, sex, age or self-perceived skin sensitivity by compiling data from multiple studies. This would provide a larger number of test subjects to examine and also determine whether results seen with multiple chemicals would show any degree of consistency in the patterns of response.

Previous racial comparison studies have been based upon direct 2- or 3-population comparisons within individual studies. Though occasional differences in acute irritation responses were observed (e.g. increased reactivity in Japanese versus Caucasian subjects), it was not a consistent finding (4, 9). Such variation in response among individual small-scale studies is not uncommon in the litera-

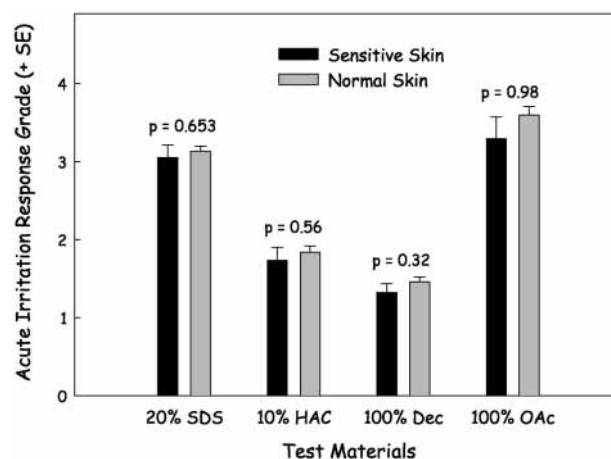


Fig. 5. All test subjects responded to the following question during their recruitment survey: “Do you believe you have sensitive skin? If so, why?” The mean acute skin response grades ($\pm$ SE) were compiled separately for all subjects answering yes and no, respectively. The mean grades for both groups for all four chemicals were cross-compared by statistical analysis. The numbers of normal skin and ‘sensitive’ skin subjects tested with each chemical were: SDS (331 normal; 53 sensitive), Dec (227 normal; 52 sensitive), HAC (205 normal; 53 sensitive), OAc (118 normal; 17 sensitive). One HAC-treated subject did not have a response listed for the question and was omitted from the analysis.

ture (3). The compilation of results across multiple studies provided a different means to approach this question. In this analysis, there was a consistent trend toward increased reactivity (i.e. reduced time to respond) observed in the Asian versus Caucasian subjects. There is no presumption that the subjects included in this analysis were representative of their respective populations at large; however, the much larger number of subjects evaluated (>200 versus typical studies of 40 or less) lends some support to the perception of increased reactivity in Asian versus Caucasian subjects.

The comparisons of male versus female responses also showed consistent differences in skin reactivity. Significant or directional increases in acute skin irritation grades (and reduced TR_{50} values) were seen in the male subjects with all four chemicals examined. Though there is often a perception that females are more reactive to skin irritants than males, this is commonly based on epidemiological assessments, which introduce differences in chemical exposure patterns. It is not generally supported by direct comparative testing (19–21). The finding of slightly increased reactivity among the male subjects in the current comparative analysis should not be over-interpreted to indicate a general increase in male skin reactivity. However, these data clearly do run counter to generally unsubstantiated claims of increased reactivity in females.

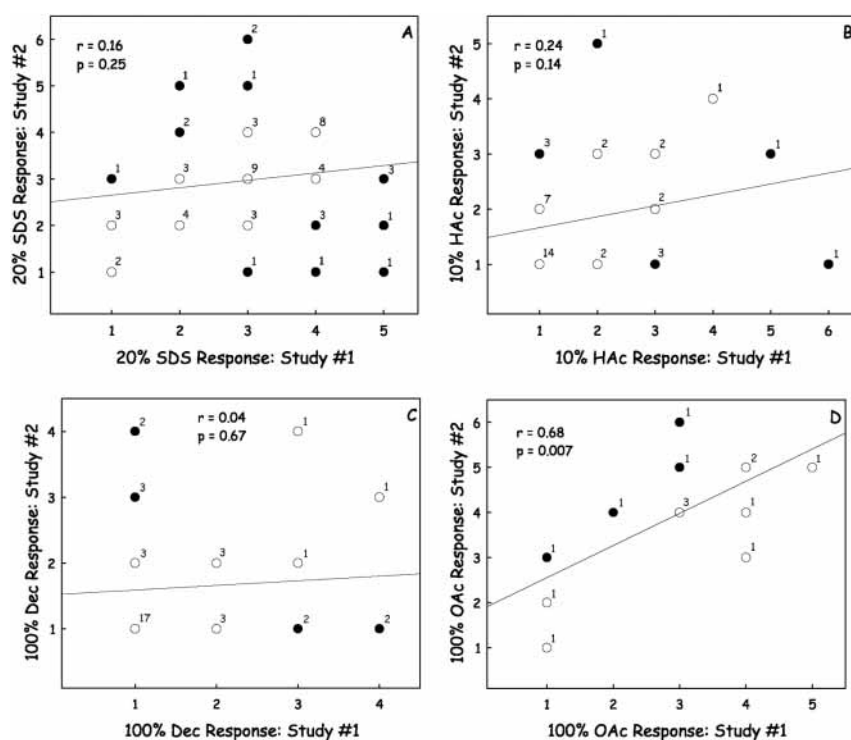


Fig. 6. Patch test responses were compiled from individual subjects exposed to the same chemical in two or more studies. The acute irritation grades were plotted for each cross-study comparison and data were examined by linear regression analysis. The number above each symbol indicates the number of individual subjects showing each response pattern. Filled symbols designate matched responses that differed by 2 units or more.

In the study of the effects of age on skin irritation responsiveness, there have been reports of a reduced reactivity among older versus younger test subjects (3). This has been most commonly observed in studies comparing widely disparate age clusters (22–24). The results presented here also indicated a significant or directional reduction in the irritant reactivity of older (>55 years) test subjects compared to various younger age clusters. Thus, there may be sufficient evidence accumulating from multiple studies conducted over the years to lend credence to the general belief that irritant skin reactivity declines with advanced age (19, 21).

The question of irritant skin reactivity in relation to self-perception of skin 'sensitivity' has been difficult to gauge, in part because of variation in subjective assessment methods employed. Though it is recognized that, at the individual subject level, perception of 'sensitive skin' does not always equate with enhanced reactivity to chemosensory stimuli (25), some studies have shown slightly increased sensory irritation responses among subjects previously claiming increased skin reactivity to various recall or imagined stimuli (25, 26). In contrast, other studies suggest no relationship between self-assessed skin sensitivity, or actual reactivity to chemosensory probes, and *objective erythematous* reactions to skin irritants such as SDS (9, 27). In the current study, subjects professing to have 'sensitive skin' did so for a variety of reasons ranging from perceptions of product intolerance to

prior testing with chemical probes such as lactic acid (9, 28). However, in comparing actual skin reactivity to the four chemicals, the objective responses observed were virtually identical in the 'sensitive' and 'normal' skin populations.

Of course, the overall question of population differences in skin reactivity is highly dependent upon the degree of variation in response *within given populations* as well as *within individual subjects* in a population. A normal distribution of reactivity within a given population is a common finding in skin irritation studies (3) and was clearly manifest in the current analysis when the overall population response to SDS was plotted (Fig. 1C). Interindividual difference in irritant skin reactivity is common, even within fairly homogeneous groups of subjects (1). Moreover, evaluating an individual subject's responses to different stimuli within studies has shown frequent divergent response patterns (2, 9, 13). In the current study, we extended this observation by demonstrating that the results of repeat tests of individuals to the same chemicals across different studies tended to show absolutely no correlation. The only exception was in the comparison of a small number of subjects to a strong irritant in two studies conducted only a few months apart. This reinforces the conclusion from these past studies that a subject's reactivity to a given chemical is not necessarily predictable from their reactivity to other chemicals or to the same chemical in previous tests.

Understanding individual variation and population differences in skin reactivity has been, and will continue to be, an important consideration in product and ingredient skin safety testing and risk assessment. The more relevant information that can be developed to explore this question, the better these assessments will be. It is important to note that relatively small skin response differences, as reported here, should not be viewed as justification for mandating population-specific safety testing, especially when other available data (e.g. exposure, habits and practices, use test) support adequate margins of safety. As it stands today, the general findings from studies on this subject tend to support current well devised and documented skin safety testing and risk assessment procedures, with the proviso that such procedures be flexible enough to account for possible population differences wherever and whenever they might be relevant (3).

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