

Racial differences in acute and cumulative skin irritation responses between Caucasian and Asian populations

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One of the more confounding issues in dermatology relates to racial differences in susceptibility of human subjects to skin reactions resulting from chemical or physical trauma. There is some historical evidence to support a greater resistance of Black versus Caucasian populations to skin irritation or skin allergy, likely due to a more substantial barrier to chemical penetration. A heightened sensitivity among Asian subjects (versus Caucasians) has been suggested; however, the evidence published to date is not very compelling. Part of the difficulty has been the lack of concurrent studies. Previously, we had examined the elicitation of mild skin irritation responses to relatively high concentrations of test chemicals, using a novel acute irritation patch test protocol for the assessment of chemical skin irritation potential. Caucasian and Chinese subjects were exposed under patch for up to 4 h to chemicals of varying irritation potency. No significant differences were seen in the cumulative incidence of positive responders to any of the test chemicals across the 2 populations, even when the subjects were preselected for sensitivity to lactic acid stinging. To extend these findings, the focus of the current investigation was to compare directly skin irritation responses between Caucasian subjects and different subpopulations of Asian subjects (Chinese, Japanese) to determine if any significant differences in response patterns would emerge. 2 separate studies were conducted. The initial study compared Caucasian and Japanese subjects for responses to 20% sodium dodecyl sulfate (SDS), 10% acetic acid, 100% octanoic acid, 100% decanol, and water. In addition, a concurrent test was conducted comparing 14-day cumulative irritation responses to varying concentrations (0.025% to 0.3%) of SDS. In both the acute and cumulative irritation tests, the Japanese subjects showed a tendency to respond faster than the Caucasian subjects. Significant differences in response were seen at several chemical exposure time points in the acute irritation test, and with the lowest concentration of SDS (0.025%) in the cumulative irritation test. A repeat of this exact study protocol was then conducted among Caucasian, Japanese, and Chinese subjects. In this 2nd study, no differences were seen in the acute or cumulative irritation responses between the Japanese and Caucasian subjects. The Chinese subjects showed a heightened response to 10% acetic acid (after 4 h of exposure), but otherwise displayed a similar response profile in the acute irritation test. They showed a slower and less severe response in the cumulative irritation test compared to the Caucasian or Japanese subjects. These divergent results underscore the difficulty in ascribing true population-based differences in skin reactivity based upon studies in limited subject populations. It may be possible to detect differences in individual studies, but repeat testing may fail to confirm a consistent trend. These findings may be indicative of the wide variation in skin responsiveness across human subjects in general.

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Prior to the introduction of new products or product ingredients into the marketplace, a skin safety testing and risk assessment process is required to insure skin compatibility under a variety of potential exposure conditions. The safety testing process involves development of data from various pre-clinical and human studies. Risk assessment entails

the evaluation of these data in the context of all reasonably foreseeable human exposures and benchmarking against other similar products or ingredients. Several thorough reviews of this process as it relates to the assessment of skin sensitization have been published (1–3), as well as an illustrative example of the process (for both skin sensitization

and irritation) related to the development of a transdermal drug product (4).

Underlying this testing and risk assessment process is one of the fundamental questions that pervades the field of dermatotoxicology; whether diverse human populations differ in respect to their susceptibility to adverse skin effects such as skin irritation or skin sensitization due to chemical exposures or physical insult. As companies increasingly market products globally, this question impacts directly on the approaches used to assess skin safety and risk. A recent review on this question underscored the fact that there is little documented evidence of population differences in skin biology or reactivity and that current clinical skin safety testing procedures (which focus primarily on the testing of Caucasian female subjects) are fairly conservative (5). Hence, there is little scientific justification at present to mandate population-specific skin safety testing. Still, there are considerable knowledge gaps that need to be addressed to fully understand how different populations (race, age, and gender) compare in their reactivity. This is particularly relevant with regard to racial differences in skin reactivity between Caucasian and Asian populations.

Specific to skin irritation responsiveness, there are some conflicting data in the literature on the relative susceptibility of Caucasian and Asian populations to irritant chemical exposures. While there has been speculation that Asians are more reactive to skin irritants (6, 7), the data from actual comparative studies are far less compelling. A 15-year-old study by Rapaport (8) is the only example from the English language literature that shows a greater irritant response among Asian (Japanese) subjects. His study utilized a cumulative irritation patch test protocol and showed increased reactivity in Japanese versus Caucasian subjects. It is not clear from the publication whether the populations were tested concurrently. There are additional data from the Japanese literature which also report an increased reactivity in Japanese subjects (9, 10). In the latter 2 studies, the conclusions were clearly confounded by the fact that the comparisons were made across different geographical locations and from studies that were not conducted concurrently. More recently, studies on the acute skin irritation responses to high concentrations of various irritant chemicals (11, 12) have been conducted among different Caucasian and Chinese populations. Initial studies, conducted under a common protocol but at different geographical locations (13), failed to show an increased reactivity among the Chinese subjects to the anionic surfactant, sodium dodecyl sulfate. Subsequent studies were conducted under the same common protocol, but

involved concurrent testing of both Caucasian and Chinese subjects with several irritant chemicals (14). These studies also failed to demonstrate a consistent difference in skin reactivity between populations.

Part of the reason for the disparate results among the studies cited above might be attributable to the different protocols used (acute irritation versus cumulative irritation patch tests) or the different Asian populations studied (Japanese versus Chinese). Also, the well-known variability in human skin irritation responsiveness in general (13–15) might contribute to variable results seen between, even carefully controlled, studies. The current studies were undertaken to address some of the disparity seen in the previous studies cited above. In an attempt to address the questions surrounding Asian population subtypes and skin irritation test methods, we employed a multi-parameter approach; using both acute and cumulative skin irritation test protocols concurrently in test populations comprised of Caucasian, Japanese, and Chinese subjects.

Materials and Methods

Chemicals

Test chemicals studied included sodium dodecyl sulfate (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) and were at least 99% pure. Lack of corrosivity of the test materials (under conditions of the test protocol) was assured prior to testing via reference to published data (16–18).

Human patch test procedures

All clinical testing was conducted at the California Skin Research Institute (San Diego, CA) 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 one study, 31 Caucasian subjects (4 male/27 female) and 20 Japanese subjects (8 male/12 female) (ages 18–69 years) were impaneled. 3 Caucasian subjects were dropped from study participation prior to study completion. In the 2nd study, 18 Caucasian subjects (6 male/12 female), 18 Japanese subjects (4 male/14 female), and 16 Chinese subjects (8 male/8 female) were impaneled (ages 18–70 years). 1 Japanese and 1 Chi-

nese subject were dropped from study participation prior to study completion. All of the subjects who dropped from the 2 studies did so because of reasons unrelated to the studies per se and no one dropped out because of adverse skin reactions.

Acute irritation patch test

Study subjects were exposed on the upper outer arm to each test material for up to 4 h according to previously described procedures (11, 12, 14, 18, 19). In each study, 20% SDS was tested as a positive control and dH₂O was tested as a negative 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). 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 5 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 24, 48, and 72 h 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 sole 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 pro-

cedure were intended to avoid the production of strong irritation responses. Greater than 90% of all skin reactions were mild in severity and resolved quickly.

Cumulative irritation patch test

In parallel with the acute irritation patch tests, all study subjects were concurrently exposed to each of 4 concentrations of SDS (0.025%, 0.05%, 0.1%, and 0.3%) on the upper back for 14 consecutive days. Each SDS concentration was applied in 0.2 ml volumes to 25 mm Hill Top chambers. Each patch was worn for 24 h, then removed and the skin sites graded 15 min after patch removal. The sites were graded using a 7-point scale of increasing irritation.

- 0 no reaction
- 1 minimal (barely perceptible) erythema
- 2 mild but well defined erythema only
- 3 moderate erythema only or mild erythema plus edema and/or papules
- 4 severe erythema only or moderate erythema plus edema and/or papules
- 5 severe erythema plus edema and/or papules or any vesicular reaction
- 6 bullous reaction or any grade 3–5 skin reaction that spreads beyond the patch site

New patches were then applied at the same sites. Once a skin grade of ≥ 3 (moderate erythema or mild erythema plus edema and/or papules) was assigned to a patch site, no further patches were applied and a grade 3 was carried out for the remainder of the study for data evaluation purposes. However, the laboratory continued to grade these skin sites for the duration of the 14-day period, enabling the assessment of skin recovery.

Data analysis

For the acute irritation patch test, the effective number of panelists completing the test included all subjects who received a 4-h exposure to that test material, plus any subjects for which 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 data were compiled as the cumulative % incidence of positive skin reactions to a given test material. Responses to the various test materials in a given study were compared to one another using the Fisher's exact test. The temporal responses were also evaluated by curve fitting (SigmaPlot for Windows, version 4.0) and TR₅₀ values (the time of exposure necessary for 50% of the exposed population to show a positive skin response) were determined.

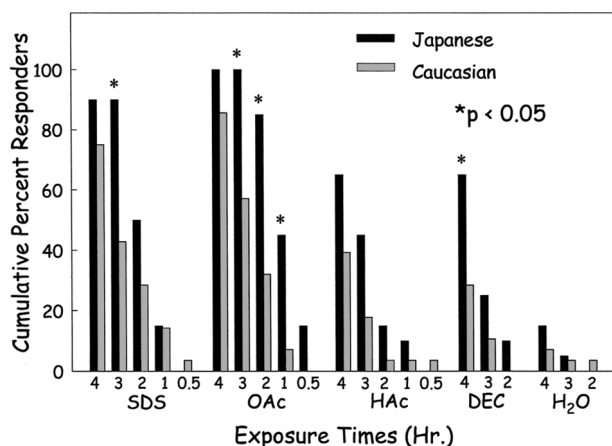


Fig. 1. Separate panels of Caucasian ($n=28$) and Japanese ($n=20$) test subjects were exposed to irritant materials in a single side-by-side study. Based on the cumulative response incidences at each time point examined, there were 5 exposure times with 3 test materials (SDS, OAc, DEC) at which the Caucasian population response was significantly less than the Japanese population response (*). Several additional exposure time/test material combinations showed directionally reduced Caucasian population responses.

For the cumulative irritation test, the skin grades assigned to each subject at each visit were summed (for all subjects in the test population) as the cumulative irritation score for each time point. The temporal response for each subject population and SDS concentration was then determined by curve fitting (as above) and TR_{50} values derived. An irritation index was also calculated by summing each subject's grades for all time points and dividing by 42 (theoretical maximum cumulative grade if a cutoff grade 3 were assigned for all 14 grading time points). Population differences in the calculated irritation index, for each SDS test concentration, were evaluated for statistical significance using student's t -test.

Results

An initial study was conducted to compare the acute irritation response of Caucasian and Japanese subjects to various chemical exposures (20% SDS, 10% acetic acid, 100% octanoic acid, 100% decanol, and distilled water). The chemicals were selected based on prior knowledge that they produce a wide range of cumulative responses, over exposure periods of 1 to 4 h, in the acute irritation patch test (14, 18, 19). As described in Materials and Methods, each test subject received repeated occluded patch exposures to each chemical for durations of 0.5 to 4 h, or until any magnitude of positive response occurred. The data were recorded as the percent cumulative incidence of posi-

tive responses in each subpopulation, at each exposure time point. Differences in response to each chemical at each time point were compared by the Fisher exact test. Also, the time response values obtained enabled the calculation of a TR_{50} value, the time of exposure required for 50% of all test subjects to respond to that chemical. The results of this study are shown in Figs. 1 and 2.

Fig. 1 shows the comparative incidence of positive responders from both study populations for each chemical and exposure time point. In general, the Japanese study population showed greater cumulative responses for all of the chemical treatments and at several exposure time points. Statistically significant increases in the Japanese subjects' response was seen for five different chemical/exposure time comparisons denoted by the asterisks

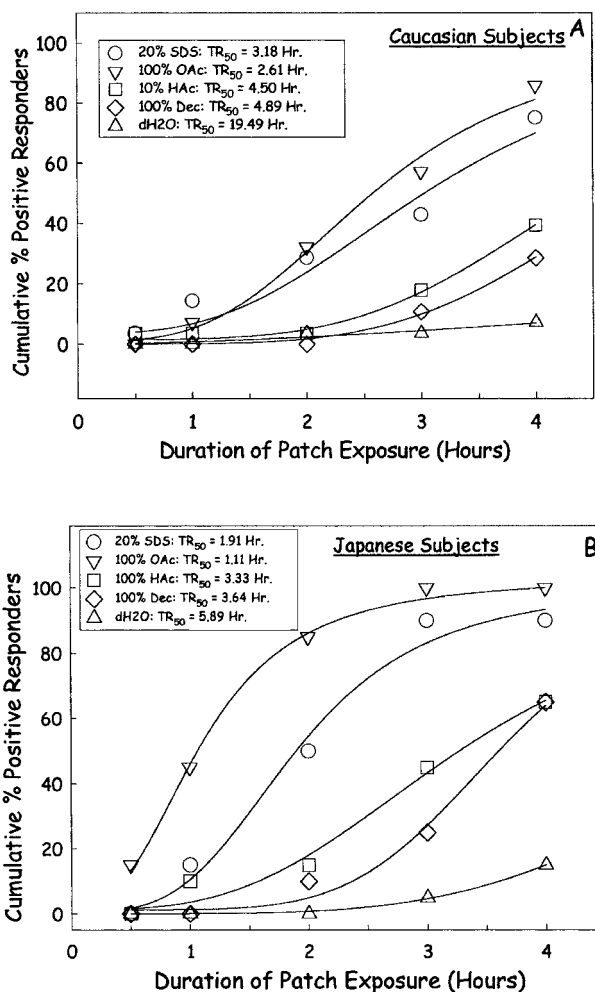


Fig. 2. The acute irritation responses at each exposure time point are presented for the Caucasian (A) and Japanese (B) subjects. A logistic 4-parameter curve was fit to these data points and a TR_{50} value obtained for each chemical irritation response. This value represents the exposure time for each chemical to produce a positive skin reaction in 50% of the study population.

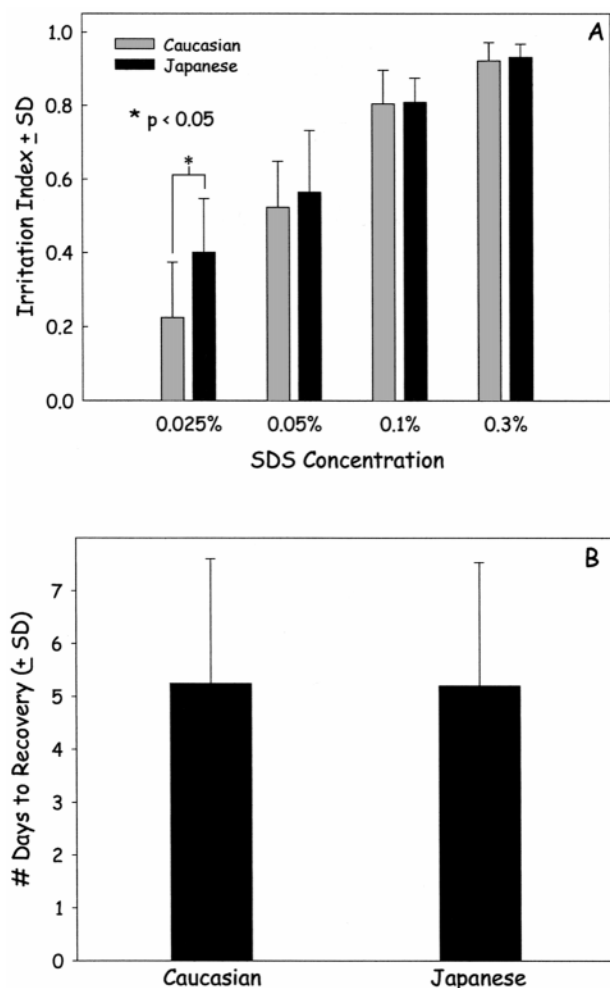


Fig. 3. Separate panels of Caucasian ($n=28$) and Japanese ($n=20$) test subjects were exposed to 14 consecutive 24-h patches of a series of SDS concentrations (0.025%–0.3%) in a single side-by-side study. Once a subject received a skin grade of ≥ 3 , no additional patches were applied and a grade of 3 was carried out for the remainder of the 14 days. The irritation index (A) was then calculated for each subject as described in Materials and Methods. The asterisk (*) indicates that, for the 0.025% SDS concentration, the Caucasian subjects had a significantly lower response. For the highest SDS concentration, a calculation was also made of the time (days) needed for the skin reaction to resolve (to grade 1) after first reaching a grade ≥ 3 . These data were used to compute a days-to-recovery value for each population (B).

(*) in Fig. 1. Several other comparisons showed directional differences. The increased reactivity among the Japanese subjects was also apparent in their speed of response (Figs. 2A, B). For each chemical, the calculated TR_{50} value was at least 1 h shorter for the Japanese test subjects.

Individual responsiveness to skin irritation is a function of both the dose of the chemical and the duration of exposure. To determine whether differences in skin reactivity between populations was strictly a function of a certain type of exposure

(i.e., high concentration/short duration), the same study subjects recruited for the acute irritation study were also tested for their reactivity to low concentrations of SDS in a protracted cumulative irritation test. This study involved daily (24 h) occluded patch exposures to very low concentrations of SDS (0.025–0.3%). The patches were reapplied each day to the same skin site for a period of 14 days, or until a moderate level of skin irritation was produced. If the latter occurred, then no additional patches were applied and the final skin grade assigned was carried out to the end of the study for calculation purposes (see Materials and Methods). Whereas the acute irritation patches were applied to the upper arm, the cumulative irritation patches were applied to the upper back. The results of this study are shown in Figs. 3 and 4.

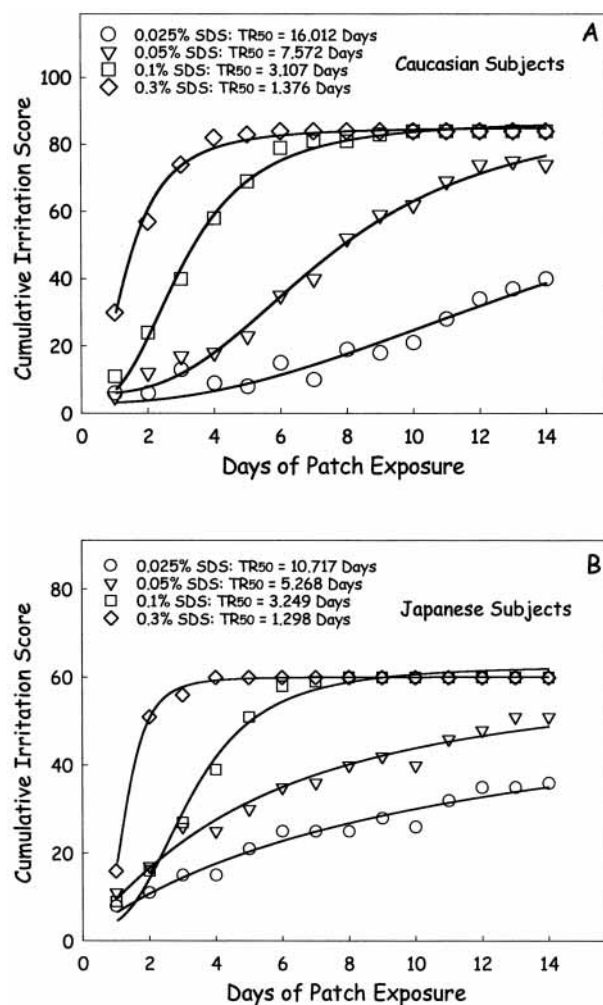


Fig. 4. The population time response comparisons for each SDS test concentration were made by summing the skin grades for each day across all subjects within the Caucasian (A) and Japanese (B) populations. TR_{50} values were determined by curve fitting and represent the exposure time in days necessary for the population to reach a $1/2$ maximal skin irritation grade.

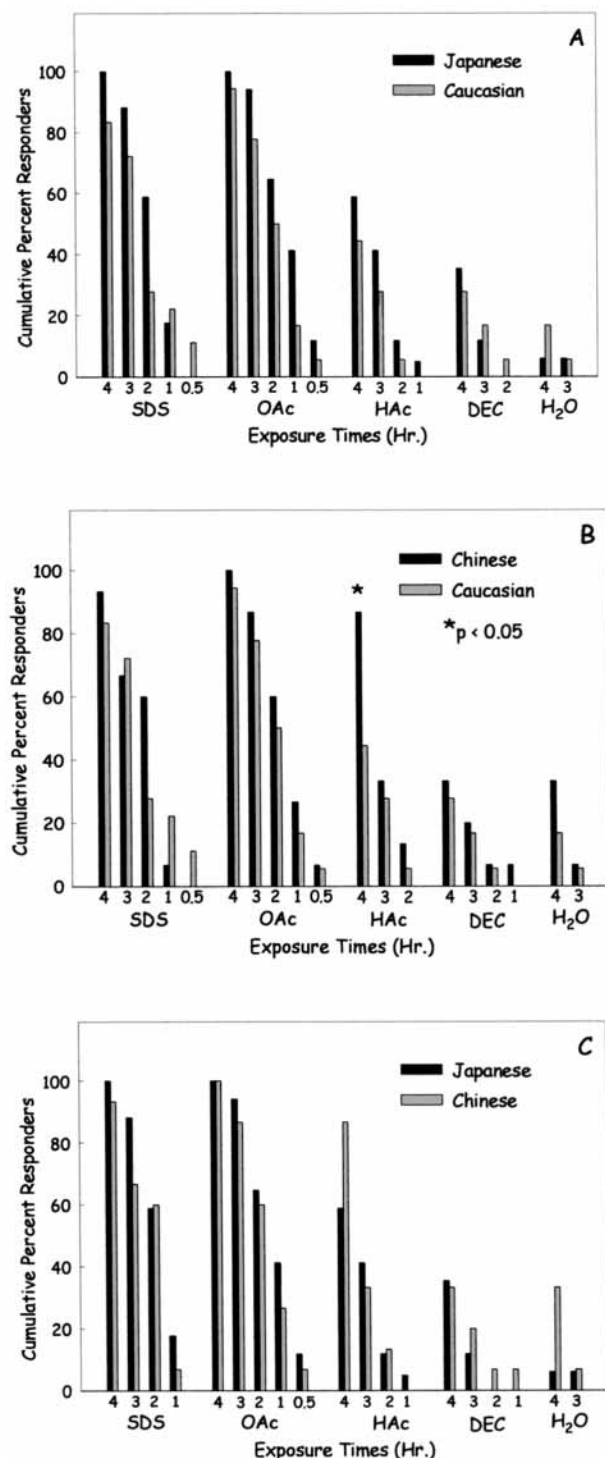


Fig. 5. Separate panels of Caucasian ($n=18$), Japanese ($n=17$), and Chinese ($n=15$) test subjects were exposed to irritant materials in a single side-by-side study. Shown in the figure are the dual comparisons of Japanese vs. Caucasian subjects (A), Chinese vs. Caucasian subjects (B) and Japanese vs. Chinese subjects (C). Based on the cumulative response incidences at each time point examined, there was only a single exposure time/test material condition that demonstrated a statistically significant difference in response between populations (*). Overall, there was no consistent pattern of heightened or diminished reactivity by any of the 3 study populations.

The irritation index is a calculation that reflects the entire test population's response to each concentration of SDS relative to the maximum possible response that could be recorded. This is shown in Fig. 3A for the Caucasian and Japanese populations. No difference in response was seen at the 3 highest concentrations. However, at the lowest concentration (0.025%), the Japanese population had a significantly greater response. At the highest SDS concentration (0.3%), all subjects in both populations reached the highest permitted skin grade (3) before the end of the study, and all those skin grades had resolved to 1 or 0 by day 14. By comparing the time (in days) for each subject's skin reaction to resolve to grade 1, an assessment could be made of the difference, if any, in population skin recovery time. As shown in Fig. 3B, there was no difference in recovery time.

As in the case of the acute irritation test, the summing of the cumulative irritation grades for all subjects on each day of the study allowed for the determination of a TR_{50} value, the time of exposure (in days) required for the overall test population to reach a half maximal response. The calculated values for the Japanese and Caucasian test subjects are shown in Fig. 4. Consistent with the irritation index results, a difference in response rate was seen primarily for the lowest SDS concentration, with a slight difference also seen at the 0.05% concentration. In both cases, the Japanese subjects reacted more quickly. The 2 highest concentrations showed equal TR_{50} values.

This comparison study of Caucasian and Japanese subjects provided 2 major findings. The cumulative irritation test data tended to concur with earlier studies (8) that Japanese subjects were more reactive in such studies, in this case at least to the lower SDS concentrations. The acute irritation portion of the study also provided the 1st demonstration of an increased reactivity among Asian subjects in acute chemical irritation testing, a result not seen in earlier testing of Caucasian and Chinese subjects (13, 14).

Because of these diverse results, a 2nd identical study was conducted approximately 4 months after the completion of the 1st study. In this case, a 3rd population (of Chinese test subjects) was included. This design would determine whether the differential reactivity was common across Asian populations or whether there might be response heterogeneity among Asian sub-populations. The test chemicals and exposure protocols were identical to the 1st study. Also, the weather conditions during the 2 periods were similar.

Fig. 5 shows the results of the acute irritation portion of the study. Unlike the 1st study, there was no significant difference in acute irritation to

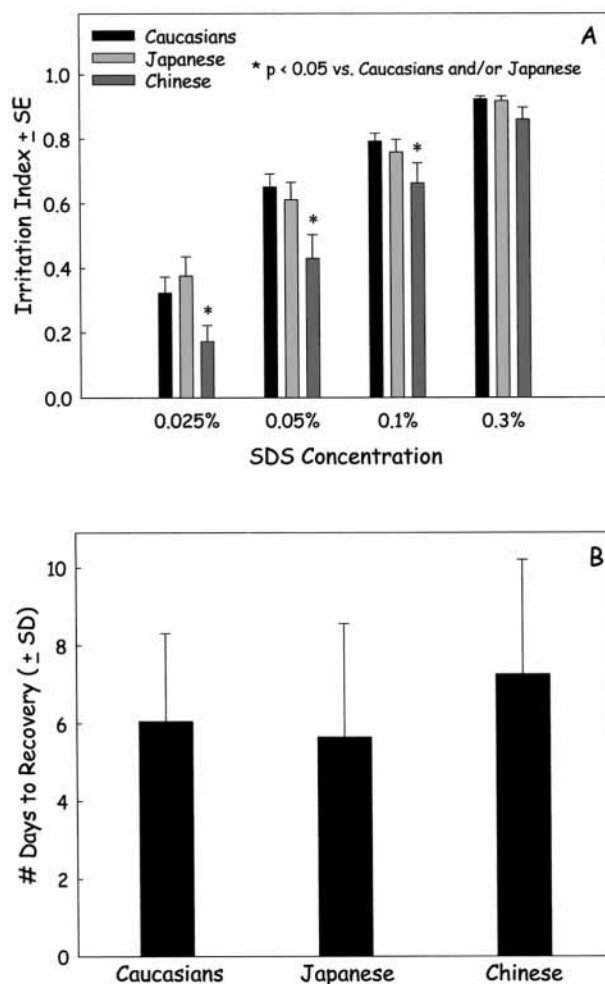


Fig. 6. Separate panels of Caucasian ($n=18$), Japanese ($n=17$), and Chinese ($n=15$) test subjects were exposed to 14 consecutive 24-h patches of a series of SDS concentrations (0.025%–0.3%) in a single side-by-side study. Once a subject received a skin grade of ≥ 3 , no additional patches were applied and a grade of 3 was carried out for the remainder of the 14 days. The irritation index was then calculated for each subject as described in Materials and Methods. The Chinese population showed a significantly reduced irritation index at all but the highest SDS concentration (A). For the highest SDS concentration, a calculation was also made of the time (days) needed for the skin reaction to resolve to a grade of 1. These data were used to compute a days-to-recovery value for each population. There was no difference in time to recovery between any of the study populations (B).

any of the test chemicals between the Japanese and Caucasian test subjects (Fig. 5A). Some directional differences were seen, but they went in both directions; in some cases the Japanese subjects were slightly more reactive and in some cases the Caucasian subjects responded to a greater extent. The Chinese/Caucasian comparison is shown in Fig. 5B. In this comparison, the only significant difference was a greater response among the Chinese subjects to acetic acid at 4 h. The Japanese/Chinese

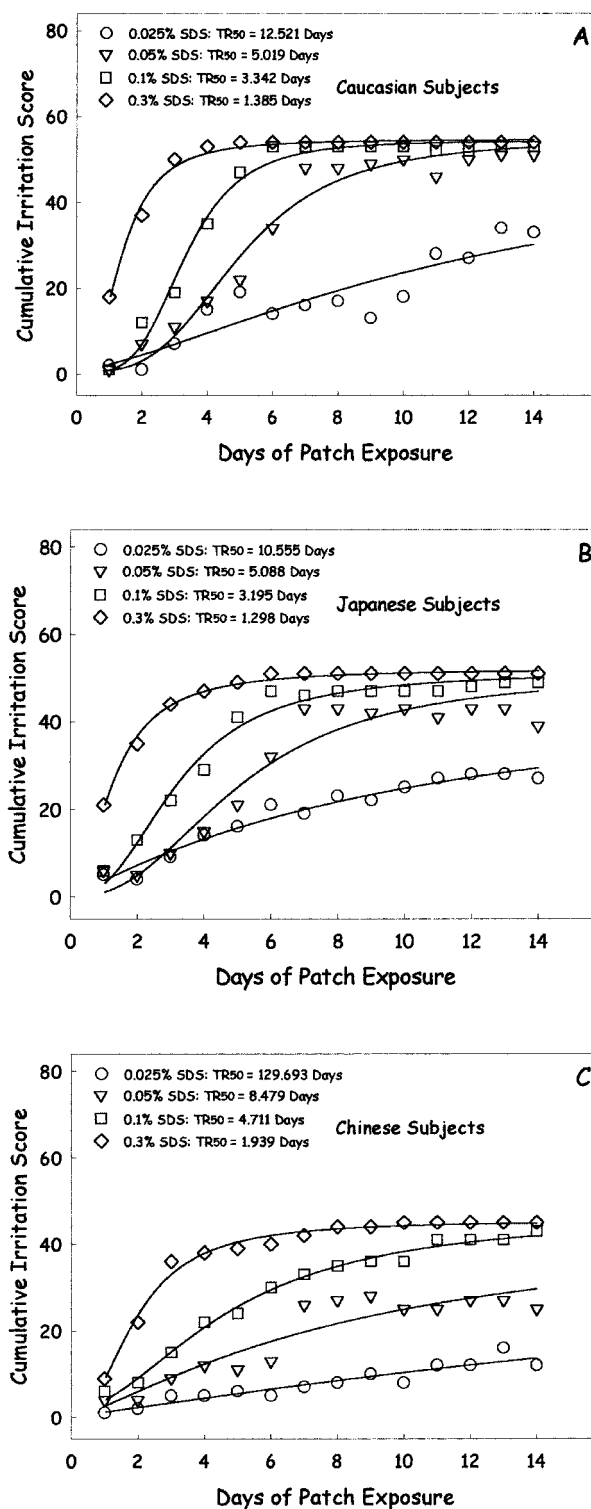


Fig. 7. The population time response comparisons for each SDS test concentration were made by summing the skin grades for each day across all subjects within the Caucasian (A), Japanese (B), and Chinese (C) populations. TR_{50} values were determined by curve fitting and represent the exposure time in days necessary for the population to reach a half maximal skin irritation grade. The Caucasian and Japanese populations showed very similar time response profiles at all SDS concentrations, with the Chinese population having slower responses at all concentrations.

comparison showed no significant differences. The time response profiles (TR_{50} values) for the acute irritation test were more similar across the 3 study populations (<1 h difference in TR_{50} values for most irritating materials) than had been observed between the Caucasian and Japanese populations in the 1st study (data not shown). This was in keeping with the lack of significant differences in the total cumulative incidence of responses.

The cumulative irritation data for this study are shown in Figs. 6 and 7. The irritation indices shown in Fig. 6A showed nearly identical patterns of response between the Japanese and Caucasian populations, again in contrast to the previous study. The only significant difference seen among the study populations was a significantly reduced response among the Chinese subjects at the 3 lowest SDS concentrations. As in the 1st study, there was no difference between the populations in time for grade 3 skin reactions to resolve to grade 1 (Fig. 6B).

The time response patterns for the cumulative irritation test are shown in Fig. 7. In this study, there was no discernible difference between the Caucasian and Japanese populations in their overall time response patterns (Figs. 7A, B). This was largely attributable to a faster response by the Caucasian subjects versus the earlier study, as the Japanese subjects' temporal response pattern was virtually identical to the earlier study (compare Figs. 4 and 7). In keeping with the results shown in Fig. 6A on irritation index values, the Chinese population was the slowest to respond in this study, showing greater TR_{50} values at each SDS test concentration (Fig. 7C).

Discussion

The skin safety assessment of new ingredients and product formulations is a critical process prior to the introduction of new or reformulated products onto the market. A variety of clinical test methods have been developed and used over the years to support this assessment, particularly in the areas of acute and cumulative skin irritation and skin sensitization (1–4, 20, 21). The clinical tests, especially those involving finished products, are conducted not to “predict” a dermatotoxic response, but for the purpose of confirming safety under an exaggerated exposure condition. An acceptable outcome, particularly when compared to other safe and successful products of similar type or composition, provides the support for further development or marketing (1). An unfavorable outcome can lead to stopping the development effort for a new product or ingredient (4).

Critical to this process is the underlying assumption

that the clinical study population is generally representative of the user population, at least in terms of their potential to develop adverse skin responses. This consideration is magnified in an era of global marketing of products, where the end users are incredibly diverse in terms of race, age, sex, skin type, culture, and the habits and practices associated with use of different products. Recent guidelines from the European cosmetic trade association (COLIPA) intimated that the skin compatibility assessment of finished products be done on subjects, the sex, age, ethnic origin, and skin types of whom are “in accordance with the appropriate user group of the product to be tested” (22). There have also been reports in the scientific and trade literature speculating on the differential skin reactivity of different racial subpopulations, particularly in regard to a presumed increased skin reactivity among Asian versus Caucasian populations (7, 23).

A recent review on population differences in skin reactivity summarized decades of literature on this topic (5). It indicated that there clearly are some consistent differences in skin reactivity noted in the literature. These are principally associated with a reduced reactivity among Black subjects versus Caucasian subjects, due to apparently stronger skin barrier properties. Otherwise, most of the population differences reported have been difficult to reproduce or reported only in isolated studies with limited controls or follow up. The conclusion stated in this review was that skin safety testing as practiced today, which focuses largely on female Caucasian test subjects, is a sensitive and conservative approach. While population-specific safety testing might be appropriate in certain situations, there is no credible scientific justification to mandate this approach as a general requirement (5).

Why then is there the interest in continuing to investigate population differences in skin reactivity? The issue relates to the tendency, in the lack of definitive data, to assume that the differences are real. Admittedly, there are significant data gaps in our knowledge of population differences in dermatotoxicology. The gaps include limited study methods, limited population (and subpopulation) comparisons, and a limited number of test materials that have been studied. The purpose of the studies reported here was to address some of these gaps by combining different test procedures, for both acute and cumulative skin irritation, multiple chemicals of varying reactivities, and different Asian as well as Caucasian test subjects.

Earlier work from our laboratory had failed to show a difference between Caucasian and Chinese test subjects in their acute skin irritation response

to 4 different test chemicals of differing irritation potencies (14). This finding was consistent regardless of whether the test subjects were unselected or initially subdivided into lactic acid-sensitive or -insensitive subpopulations. Because of a literature study reporting that Japanese subjects were more reactive than Caucasian subjects in cumulative irritation patch tests (8), we next chose to examine, in parallel, both acute and cumulative irritation responses in Caucasian and Japanese test subjects. This was done to address 2 important variations between our earlier work and the studies of Rapaport (8), the methodology difference (acute versus cumulative irritation) and the population comparison (Japanese versus Chinese).

In both the acute and cumulative phases of this study, the Japanese subjects showed both faster-developing responses and a higher incidence of responses than the Caucasian subjects (Figs. 1–4). The acute patch test results were clearly different than what we had shown earlier in our Caucasian versus Chinese test populations. It should be noted that the TR_{50} values derived for the Japanese population were in the range seen previously for these chemicals (14, 18, 19). This points to the importance of conducting parallel comparison studies rather than comparing results to historical data. The cumulative irritation data tended to confirm, in part, the earlier results of Rapaport (8). He also included SDS (0.5% and 4%) in his testing regimen. However, where the difference in response in our study was magnified at the lower SDS concentrations, he saw a greater difference at the highest concentration tested. Interestingly, his SDS test concentrations were an order of magnitude greater than ours. We would not have been able to test the concentrations he reported due to too severe a skin irritation response. In spite of the differences seen in the kinetics and magnitude of the skin reactions between the 2 populations, there was no difference in time to recovery in the cumulative irritation study (Fig. 3B).

To see if these study results could be confirmed, and to further examine possible differences in skin reactivity between the Chinese and Japanese subjects, a 3-population study was conducted under an identical protocol, comparing all 3 study populations in concurrent testing. In this study, the acute irritation response profile was similar among all 3 populations. The data from all 3 populations were within historical norms and there was no consistent finding of increased or decreased sensitivity for any population (Fig. 5). The Chinese subjects' increase in response to 10% acetic acid between 3 and 4 h of exposure was likely an anomaly, since 1) it was inconsistent with 2 previous studies (14) and 2) there was a similar anomalous increase in

the 4 h response to water. In the cumulative irritation phase of the study, there was, again, no confirmation of the increased reactivity among the Japanese vs. Caucasian subjects seen in the earlier study. The only significant difference was a lower magnitude (Fig. 6A) and slower (Fig. 7C) reactivity among the Chinese subjects. Again, there was no difference in time to recovery (Fig. 6B).

These data indicate that, in studies conducted on limited numbers of test subjects, significant differences in response can sometimes be detected between different study populations. That was clearly the case in the Rapaport (8) study and in our initial Caucasian/Japanese comparison study. However, repeat testing, as reported here, may fail to confirm consistent trends in differential skin reactivity and provides some explanation for the wide variation and inconsistency among literature reports on population comparison testing. As has been suggested previously (14, 18), the wide variation in response seen among human test subjects, in general, likely obscures any consistently recognizable difference in response across different human subpopulations. Clearly, more work is needed to address all the aforementioned data gaps that exist relative to this area of dermatotoxicological research. However, these results clearly underscore the potential pitfalls in ascribing to theories of population differences based only on very limited and often unconfirmed data.

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