

Ethnic variation in the skin irritation response

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There is a widespread, but largely unsubstantiated, view that certain skin types may be more susceptible to the effect of skin irritants than others. One expression of this would be that certain ethnic groups may also be more likely to experience skin irritation. As a consequence, when evaluating the skin compatibility of substances/preparations, these differences may need to be taken into account. However, other evidence indicates that, within any particular group, inter-individual variation is likely to be much larger than the differences between means for distinct groups. In this study, we have investigated 2 carefully matched panels of Caucasian and Japanese women volunteers to determine their topical irritant reaction, both acute and cumulative, to a range of materials. The results indicated that the acute irritant response tended to be greater in the Japanese panel and this reached statistical significance with the stronger irritants. Cumulative irritation was investigated only with the weaker irritants and, although again the trend was to a higher response in Japanese compared to Caucasian panelists, this rarely reached significance. Nevertheless, where risk assessment for skin irritation was critical, then at the population level, these differences might be relevant, both for safety in use of substances and products and for skin acceptability.

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For many years, there has been a perception that the skin of certain ethnic groups or of particular subsets of individuals might be more susceptible to the development of skin irritation. The original evidence relating to ethnic differences was provided through the work of Rapaport (1) in a publication which summarized a body of experience with ethnic Japanese in the Los Angeles area of the USA compared to Caucasians. This indicated, among other things, that Japanese skin might indeed be more prone to skin irritation than that of Caucasians. However, the work was not by itself definitive and other more recent studies have found little difference between various ethnic groups (reviewed in (2)). In fact, it has been suggested that, on balance, ethnic differences are relatively minor compared to the wide inter-individual variations that demonstrably do occur within a particular group (3). The same is also true when comparisons are made between various skin types (4), or between atopics and non-atopics (5). Most recently, a study of ethnic variation in the response to skin irritation showed that, in contrast to the experience of Rapaport (1), Japanese skin was not reproducibly more susceptible to skin irritation (2).

However, there are a number of shortcomings in the work described above. Firstly, some studies have investigated only the acute skin irritation response (e.g. (4)), and/or have compared responses in geographically or temporally distinct groups. Further work has other limitations, including small group sizes, groups whose ethnic origin is clear but who are no longer in the original ethnic environment (e.g., the Japanese subjects in Los Angeles (1)), or where, in order to achieve good ethnic pedigree, the study groups have been investigated in different locations at different times, so introducing several further variables into the experiment. In consequence, in the present study, we elected to investigate the acute and cumulative skin irritation response in a group of new Japanese migrants to the USA, and to compare these in parallel with a matched group of Caucasians, so eliminating most of the variables that may have complicated previous studies.

Materials and Methods

The study consisted of 2 ethnic groups, a Caucasian group and Japanese group, with 22 female

panelists in each group. The average age for the Japanese group was 42.1 years (SD 7.1 years). The average age for the Caucasian group was 40.5 years (SD 10.1 years). All the Japanese panelists were native Japanese who had been in the USA for 7–18 months and who still maintained a largely Japanese lifestyle. The Caucasian group were native Americans, though 1 originated from Germany and one from Australia. Approval by the local Institutional Review Board was obtained and all panelists signed an Informed Consent Statement. All study-related paperwork, including the Informed Consent Statement, for the Japanese panelists was translated into Japanese by a certified translator. At all times during the study, a Japanese translator was present. The study was conducted with both ethnic groups simultaneously in November 2000 at the Edgewater Test Center, Edgewater, New Jersey, USA.

Test materials consisted of 1 anionic surfactant, 1 amphoteric surfactant and 1 C8 fatty acid, all tested at concentrations of 0.3% and 0.6% based on activity, and 5 cosmetic formulations. The surfactants were sodium lauryl sulfate (SLS) (99% pure, Sigma Chemical Company, St. Louis, MO, USA), cocoamidopropyl betaine (CAPB) (38% active, sold as Tegobetaine F-50 from Goldschmidt Chemical Corporation, Hopewell, VA, USA) and caprylic acid (99% pure, Sigma Chemical Company, St. Louis, MO, USA). Volunteers selected for this study did not have any skin diseases or other signs of local irritation at the test area. The test materials were applied under occlusion to the upper outer arms of volunteers for 24 h. Hill Top chambers (25 mm, Hill Top Companies, Cincinnati, OH) were loaded with 0.2 ml of the appropriate solution or formulation. The chambers were held onto the skin with Scanpor tape (Alpharma, AS, Vennesla, Norway). Reactions were scored 6 h after patch removal using the 0–4 irritation scale shown

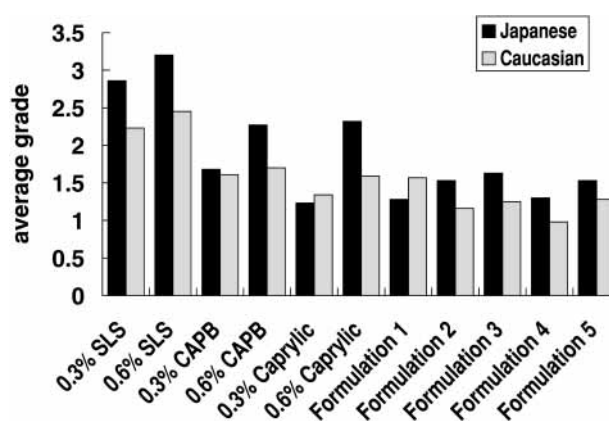


Fig. 1. The average grade of skin irritation occurring in the Japanese and Caucasian panels in response to a range of irritant stimuli applied under occlusion for 24h and scored 6h after patch removal. Differences in reactivity reached statistical significance for 0.3% and 0.6% SLS, for 0.6% CAPB and for 0.6% caprylic acid.

in Table 1. Scoring was conducted by consensus of 2 expert graders.

The 5 cosmetic formulations were also evaluated using a 4-exposure cumulative patch protocol. These materials were applied to the upper outer arms of the same volunteers for one 24-h exposure, using the same Hill Top chamber system described above. After a 6-h rest period, the test sites were scored and fresh patches were applied. Following an 18-h exposure and a 6-h rest period, the test sites were again scored. This procedure was followed for 2 additional 18-h exposure periods. If a site received a score of ≥ 2 on the grading scale in Table 1, that product was discontinued for the remainder of the study.

Any irritation reactions which occurred were followed to ensure resolution. In certain cases, post-inflammatory pigmentary changes arose and these were also followed to ensure proper panelist care.

Table 1. Details of irritation grading scheme

Grade	Detailed description
0	No apparent cutaneous involvement
0.5	Faint, barely perceptible erythema or slight dryness (glazed appearance)
1.0	Faint but definite erythema, no eruptions or broken skin, OR no erythema but definite dryness: may have epidermal fissuring
1.5	Well-defined erythema or faint erythema with definite dryness; may have epidermal fissuring
2.0	Moderate erythema, may have a few papules or deep fissures, moderate to severe erythema in the cracks
2.5	Moderate erythema with barely perceptible edema OR severe erythema not involving a significant portion of the patch (halo effect around the edges) may have a few papules OR moderate to severe erythema
3.0	Severe erythema (beet redness), may have generalized papules OR moderate to severe erythema with slight edema (edges well defined by raising)
3.5	Moderate to severe erythema with moderate edema (confined to patch area) OR moderate to severe erythema with isolated eschar formations or vesicles
4.0	Generalized vesicles or eschar formations OR moderate to severe erythema and/or edema extending beyond the area of the patch

Statistical analysis of the data was carried out using the Wilcoxon rank sum test.

Results

The studies reported in this paper comprise the acute irritant patch test response to 11 different stimuli and the cumulative irritant response to 5 materials. In Fig. 1, the results of the single 24-h patch test read at 6 h after patch removal are displayed as the average reaction grade for the Japanese and Caucasian panels. In most cases, the average grade of reaction was slightly, but significantly, higher in the Japanese group. The greatest level of reaction occurred with the 2 concentrations of SLS; with 0.6% SLS in the Japanese panel, reaction grades ranged from 2.5–4, while in Caucasians, reactions ranged from 1–3. With 0.3% SLS in the Japanese panel, reaction grades ranged from 2–3.5, while in Caucasians, reactions ranged from 1–3. A lower level of irritant reaction was seen with CAPB and caprylic acid; at the higher concentration of each of these, there was again a small but significantly higher level of response in the Japanese group. At 0.6% CAPB, reactions ranged from 0.5–2.5 in the Japanese panel, while the range was 1–2.5 in the Caucasian panel. With 0.6% caprylic acid, reactions ranged from 0.5–4 in the Japanese panel and from 1–3.5 in the Caucasian panel. With 4 of the 5 cosmetic formulations tested, the response was higher in the Japanese

group, but the difference was not significant. For the 5th formulation, the response was slightly higher in the Caucasian group, but again the difference was not significant.

Susceptibility to cumulative skin irritation in the 2 panels was examined by repeated patch testing of 5 cosmetic formulations. The results are presented in Table 2 as the average reaction grade at each time point. Each formulation induced a low to moderate level of skin irritation, with the responses following a similar pattern. Although the overall trend was for a higher level of response in the Japanese panel, this only reached statistical significance at Day (D) 2 with formulations B and C. These differences were not maintained at D3 and D4, suggesting that they may be of relatively minor importance. On only a single occasion (D1, Formulation A) was a higher response seen in the Caucasian panel.

As a consequence of the irritation induced in the 2 panels, in a small number of cases, pigmentary changes occurred. These arose only in response to the irritant substances, not to the formulations, which generally were less irritating. In total, 31 sites had some pigmentary change, out of a total of 484. The details of these reactions are shown in Table 3, together with data on their resolution at 3 months post test. The majority of the reactions (30) occurred in the Japanese panel and were hyperpigmentation in all but 3 cases. Only 6 pigmentary changes occurred in the Caucasian panel, which were an equal mix of hyper- and hypo-pigmentation; 50% of these resolved within 3 months post-testing. The changes were noticeably longer lasting in the Japanese panel, with just over 1/2 still present after 3 months.

Table 2. Cumulative skin irritation scores

	Average reaction grade (Japanese/Caucasian) on:			
	D1	D2	D3	D4
formulation A	1.3/1.6	2.0/2.0 ^{a)}	2.0/2.0	2.0/2.0
formulation B	1.5/1.2	2.0/1.8 ^{b)}	2.0/1.9	2.0/1.9
formulation C	1.6/1.3	2.1/1.9 ^{b)}	2.1/1.9	2.1/1.9
formulation D	1.3/1.0	1.6/1.5	1.7/1.6	1.7/1.6
formulation E	1.5/1.3	1.9/1.8	2.0/1.8	2.0/1.8

^{a)}Treatment was discontinued once a score of 2 was reached.

^{b)}Statistically different at the 95% confidence level.

Table 3. Pigmentary changes associated with skin irritation

Irritant	Japanese panel			Caucasian panel		
	hypo	hyper	resolved	hypo	hyper	resolved
0.6% SLS	1	9	5	2	0	0
0.3% SLS	1	5	3	2	1	1
0.6% CAPB	0	3	0	0	0	0
0.3% CAPB	0	1	1	0	0	0
0.6% CA	1	7	4	0	0	0
0.3% CA	0	2	1	0	1	1
total	3	27	14	3	3	3

Discussion

The possibility that there may exist ethnic differences in skin responses, for example to irritants, has been discussed for a number of years. Initial evidence for such differences was reported by Rapa-port (1), who showed that Japanese skin might be somewhat more susceptible to adverse reactions in comparison to Caucasian skin. However, ethnic differences have not always been apparent in skin irritation (reviewed in (2)) and this may be due, in part, to the relatively large inter-individual differences which occur within any particular grouping of skin types (see, e.g., (6)) as well as to the difficulties in controlling other variables associated with such studies. Where authentic ethnic panels have been chosen, then it is not possible to fully control the climatic conditions and/or the individuals responsible for carrying out the grading of the skin reactions (e.g., (4)). Alternatively, bioengineering techniques have been applied to avoid any subjectivity in scor-

ing, but the quality of the data produced has been limited by other factors, such as the size of the test panels (7, 8). In the present work, we have attempted to reduce to an absolute minimum many of the variables associated with such investigations by utilizing a panel of new Japanese migrants to the USA. Skin reactions in this group have been compared with that of a carefully matched Caucasian group, both groups being tested at the same time and in the same location. Thus, all variables associated with geography, climate and observer/scoring scheme have been eliminated.

The study reported herein describes both the single and the repeated application of 5 formulated materials (applied undiluted) as well as the single application of 3 substances of varying skin irritation potential, each applied at 2 concentrations. In this way, the response of both acute and cumulative skin irritation has been examined. Additionally, the panelists were carefully monitored to enable a thorough assessment to be made of any pigmentary changes associated with induced skin irritation.

All applied materials induced skin irritation to some degree. The acute irritant response was more pronounced in the Japanese panel, on 4 occasions reaching a level of statistical significance, generally these being the situations where the highest level of irritation was induced. The 5 formulations tested produced generally the lowest level of acute skin irritation, with little or no significant difference being noted between the Japanese and the Caucasian panel. Nevertheless, there was a clear trend towards a higher level of reaction in the Japanese panel. With the cumulative skin irritation response, the pattern was somewhat similar, with a general trend to a slightly higher level of reaction in the Japanese group. On 2 occasions, this reached statistical significance, although the importance of this observation is not clear, since the differences were not maintained at later time points. It could be argued that this is not such a surprising result, since none of the formulations gave significantly higher acute irritation in the Japanese panel. However, each of these formulations generated a level of irritation in both panels judged to be appropriate for repeated skin testing, whilst avoiding the risk of unnecessary degrees of skin damage.

What is the conclusion for risk assessment? Firstly, it should be noted that these results represent only a single study and thus should not be over-interpreted. Having said that, the degree of skin irritation induced in our Japanese panel was not greatly different from that in the Caucasian panel, although it was frequently higher. In the sense of hazard identification, it confirms what has been suggested earlier (4), that data from one group of human subjects is broadly applicable,

since the trends and pattern of irritation was quite similar. However, for more subtle/accurate risk assessment, where extrapolation is made from relatively small panels, then these differences might well translate into significant effects at the population level. Thus, where the risk assessment is known to be important (i.e., where there is no large built-in safety margin), skin irritation studies of the appropriate type (9, 10) carried out in the relevant population appear to be indicated. However, studies in certain ethnic groups, such as the Japanese group reported here, may bring their own issues, in this case an increased risk of pigmentary changes. These factors need to be taken into account when the study is designed, and panelists must be properly advised of these risks so that fully informed consent can be given.

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