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Effects of age on human cumulative irritation responses

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Synopsis

A 10-day cumulative irritation test was conducted to evaluate whether or not test subjects 65 years of age and older would rank eleven test materials the same as subjects 18 to 45 years of age The test materials consisted of mild to moderately irritating chemicals. The test articles were ranked similarly for both groups of subjects. Statistical analysis indicated no significant difference between the groups of subjects. Thus older subjects should not necessarily be excluded in comparative studies of irritancy.

INTRODUCTION

The 21-day cumulative irritation test is utilized to determine the irritation potential and/or comparative irritation of a wide range of topical drugs, cosmetics, cleaners, and occupational chemicals. Typically, protocols exclude subjects who are over the age of 65. This exclusion is thought to be a carryover from excluding older subjects from allergic contact dermatitis studies, as the immune system tends to decrease in its ability to respond with advancing age. However, many topical products are purchased by consumers in this age group. The aim of the present study was to determine if subjects over the age of 65 would rank potential irritants in the same order as younger persons.

METHODS

The procedure is a modification of that described by Lanman *et al.* (1) and Berger and Bowman (2). Informed consent was obtained. Two groups were evaluated: Group 1 consisted of subjects 18 to 45 years of age and Group 2 consisted of subjects aged 65 to 80. The individual samples were applied to sites on the skin of the back for contact periods lasting 24 hours. Patches were applied for five consecutive days and, following a one-day rest (Sunday), were applied for four consecutive days. Patches were removed by laboratory technicians and patch sites were evaluated 30 minutes later. Each subject

received nine applications of the test materials to the same sites. Any site reaching a maximum grade (grade 3 or 4; see Table I, scoring scale) was not repatched for the remainder of the study. The test materials are listed in Table II. Irritation was scored classically using a 100-watt incandescent blue bulb lamp as the artificial light source. The scorer was blinded as to the treatment assignments A five-point scale was used (Table I).

STATISTICAL ANALYSIS

The source data are the actual patch test scores recorded following visual evaluation of the sites on days 2, 3, 4, 5, 7, 8, 9, 10, and 11. Data used in the statistical analyses were the actual scores up to and including termination of patching. When a strong response prohibited repatching, the value at the time of termination was entered into the analyses for all scoring days till the end. Subjects that withdrew from the test were omitted from the analysis.

The following statistical analyses were performed:
1. Overall analysis comparing irritation levels of Group 1 (18–45) to those of Group 2 (65–80).
2. Analysis comparing the irritation levels of the test articles within each group.
3. Analysis comparing the irritation levels of Group 1 and Group 2 for each test article.

The patch test scores for each test article were summed across all test days for each test subject. For analyses 1 and 3, analysis of variance was utilized; for analysis 2, the overall test article scores were ranked within each subject and then analyzed using the Friedman rank sum test.

Table I
Scoring Scale

0 = No erythema visible
1 = Faint erythema
2 = Moderate erythema
3 = Intense erythema
4 = Erythema with edema, vesicles, or papules

Table II
Test Materials

A (0.2% SLS)
B (0.1% benzalkonium chloride/distilled water)
C (50% xylenes/petrolatum)
D (0.1% Retin A cream)
E (50% isopropyl myristate/petrolatum)
F (75% propylene glycol/distilled water)
G (DOAK Formula 405 AHA facial day cream)
H (Lachydrin 12 lotion)
I (OXY 10 benzoyl peroxide vanishing cream)
J (Lacticare lotion)
K (Carmol 10)

Due to test subjects being sensitized to test article I (OXY 10 benzoyl peroxide vanishing cream), the statistical analysis was conducted with this article removed.

RESULTS

The distribution of the 26 test subjects in each group is shown in Table III, and test articles were rank ordered as shown in Table IV.

The test articles were essentially rank ordered the same. Allowing for variation in a biological test should explain the flipflop in the rank ordering of test articles B and D, which were the fourth and fifth, and fifth and fourth, most irritating materials in Group 1 and Group 2, respectively.

OVERALL ANALYSIS COMPARING GROUPS

The analysis of variance indicated no significant difference between groups (p=0.1510) and no interaction of groups and test articles (p = 0.4259). A summary of the overall analysis of variance is shown in Table V.

Table III
Distribution of Test Subjects

Group 1 (18–45)		Group 2 (65–80)	
Age	n	Age	n
25–29	3	65–69	13
30–39	13	70–75	9
40–45	10	76–80	4

Table IV
Rank Order of Test Articles

Group 1 (18–45)			Group 2 (65–80)		
Rank	Test article	Test article means	Rank	Test article	Test article means
1	G (DOAK, AHA facial day cream)	24.7	1	G (DOAK, AHA facial day cream)	22.6
2	A (0.2% SLS)	22.0	2	A (0.2% SLS)	21.8
3	K (Carmol 10)	11.0	3	K (Carmol 10)	10.6
4	B (0.1% benzalkonium chloride)	10.2	4	D (0.1% Retin A cream)	7.7
5	D (0.1% Retin A cream)	8.7	5	B (0.1% benzalkonium chloride)	7.0
6	H (Lachydrin 12 lotion)	6.7	6	H (Lachydrin 12 lotion)	6.2
7	F (75% propylene glycol/distilled water)	3.0	7	F (75% propylene glycol/distilled water)	1.9
8	C (50% xylenes/petrolatum)	0.8	8	C (50% xylenes/petrolatum)	0.7
9	J (Lacticare lotion)	0.6	9	J (Lacticare lotion)	0.6
10	E (50% isopropyl myristate/petrolatum	0.3	10	E (50% isopropyl myristate/petrolatum)	0.3

Table V
Overall Analysis of Variance

Overall mean	Group 1 (18–45)	Group 2 (65–80)
	8.81	7.95

n = 26 per group.
The *p*-value for the group effect was 0.1510, indicating no significant difference between groups.

COMPARISON OF TEST ARTICLES FOR EACH GROUP

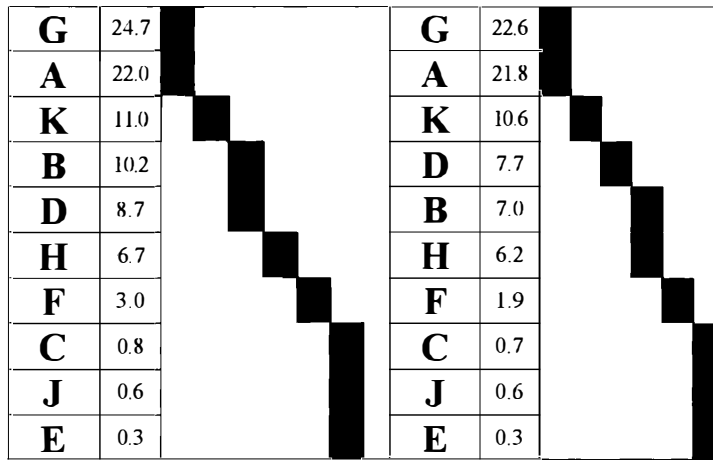
The Friedman analysis indicated significant differences between test articles for each group ($p < 0.001$). Both groups differentiated the most irritating test articles (G and A) from the remaining samples; test article K differentiated from those less irritating test articles; test articles B, D, and H differentiated from samples F, C J, and E; and test article F separated from test articles C, J, and E. A summary of these analyses is shown in Table VI.

ANALYSIS BY TEST ARTICLE

Additional analyses were conducted evaluating for differences between groups for each test article separately. There were no significant differences between groups for the

Table VI
Comparision of Test Articles for Each Group

Group 1 (18–45)		Group 2 (65–80)	
Test article	Test article means*	Test article	Test article means*
G	24.7	G	22.6
A	22.0	A	21.8
K	11.0	K	10.6
B	10.2	D	7.7
D	8.7	B	7.0
H	6.7	H	6.2
F	3.0	F	1.9
C	0.8	C	0.7
J	0.6	J	0.6
E	0.3	E	0.3
Significant comparisons at $p < 0.05$	G,A vs K,B,D,H,F,C,J,E K vs B,D,H,F,C,J,E B,D, vs H,F,C,J,E H vs F,C,J,E F vs C,J,E	Significant comparisons at $p < 0.05$	G,A vs K,B,D,H,F,C,J,E K vs D,B,H,F,C,J,E D vs B,H,F,C,J,E B,H vs F,C,J,E F vs C,J,E



* Test article means joined together are not significantly different.

Table VII
Analysis of Variance Results

Test article means	A	B	C	D	E	F	G	H	J	K
Group 1	22.0	10.2	0.8	8.7	0.3	3.0	24.7	6.7	0.6	11.0
Group 2	21.8	7.0	0.7	7.7	0.3	1.9	22.6	6.2	0.6	10.6
p-value*	>0.500	0.128	>0.500	0.228	>0.500	0.086	0.225	>0.500	>0.500	>0.500

n = 26 per group.
* No significant differences between groups for individual test article analyses.

individual test article analyses. A summary of those analyses is shown in Table VII and Figure 1.

DISCUSSION

Testing for cutaneous irritation is one of the most important aspects of cosmetic product safety development because irritancy accounts for the greatest number of complaints related to product use. Yet, little verification or improvement of the most accepted test has occurred since its inception (1,2). Our results indicate that test subjects over the age of 65 can discriminate products in a similar manner as younger test subjects.

Certainly, there will be test products that are manufactured for use by consumers younger than 65 years of age, and excluding older age subjects in the testing of those products may be appropriate. However, based on the results of this research, one can utilize subjects over the age of 65 when warranted or necessary with the assurance that

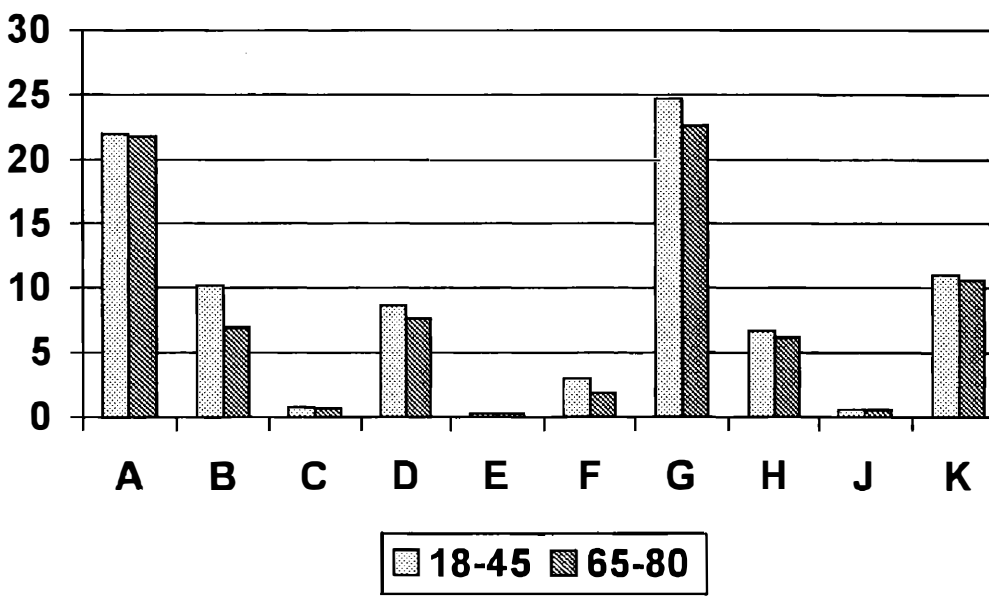


Figure 1. Patch test scores (average subject total).

test article differentiation can be achieved. We speculate that it would be appropriate to have 10% of a test panel over the age of 65, and potentially more if a product is marketed to that segment of the population.

CONCLUSIONS

Data from both groups of test subjects similarly differentiated mild to moderately irritating chemicals. The conclusions arrived at in this study indicate that older subjects should not necessarily be excluded in comparative studies of irritancy.

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