

Prevalence of patch test results from 1970 to 2002 in a multi-centre population in North America (NACDG)

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Background: The North American Contact Dermatitis Group (NACDG) has members who assess subjects with suspected allergic contact dermatitis (ACD) and patch test them with the same screening allergens using a standardized procedure permitting analysis of long-term trends in patch test reactions.

Objective: This study reports the trends in prevalence patch test positivity of allergens by pooling data collected by the NACDG between 1970 and 2002.

Patients/Methods: Patients were tested with the screening series of allergens, using a standardized technique. Data from these patients were recorded on a standard computer entry form and analysed. More than 100 allergens were tested on over 34 000 patients during several patch studies between the period. The Cochran-Armitage test of trend is used to evaluate changes in prevalence over time.

Results: 4 trends are noticed: (1) The incidence of presumed allergic nickel ($P < 0.0001$) and quaternium-15 ($P < 0.0001$) reactions rose with consistency over the years. (2) While that of cinnamic aldehyde ($P = 0.21$) and *p*-phenylenediamine ($P < 0.0001$) decreased. (3) The prevalence of positive reactions for potassium dichromate ($P < 0.0001$) shows an initial steady decrease but then a sharp increase starting from the 1996 period. (4) In contrast, thiuram ($P = 0.0008$) and neomycin ($P < 0.0001$) show an initial general increase, with a sharp decrease between 1998 and 2002.

Conclusion: Implications for opportunities to prevent ACD by utilizing less-allergenic alternatives appear robust; however, we do not wish to over generalize interpretations because of important limitations.

Key words: cinnamic aldehyde; NACDG; neomycin; nickel; nickel sulfate; patch test; potassium dichromate; *p*-phenylenediamine; quaternium; quaternium-15; thiuram. © Blackwell Munksgaard, 2007.

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Introduction

The North American Contact Dermatitis Group (NACDG), founded in 1970, has members who assess subjects with suspected allergic contact dermatitis (ACD) and patch test them with the same screening allergens using a standardized procedure so that trends in delayed-type contact sensitivity can be investigated (1–8). The results of tens of thousands of patch tests performed on patients with suspect ACD presenting with clinical disease for evaluation have been reported with the research group's initial report appearing in 1973.

Since then, the patch test figures of the NACDG have been intermittently published (1–8).

This report evaluates the trends in the results of patch testing. We retrospectively survey patch test reactions and statistically compare the results between 1970 and 2002 – in hopes of appropriately interpreting the numbers – as this has public health opportunities.

Materials and Methods

Between 1970 and 2002, over 34 000 patients having ACD were evaluated by dermatologists,

members of the NACDG, and patch tested to a tray of specified allergens (1–8). Exclusion criteria for patients included those who (1) applied topical corticosteroids near the patch test site, (2) took immunosuppressants, and (3) had medical conditions that could compromise the assessment of skin sensitization. Demographic information, clinical accounts and tabulations, and patch test reaction scoring were accumulated using standardized scoring instruments as in prior documented studies (1–8). Further details are found in Pratt et al. (1).

Statistical significance was determined with a Cochran-Armitage trend test (9) (SAS Version 8.2), which checks for trend in binomial proportions across levels of a single factor. The trend test may give strong evidence of positive or increasing linear trends or of negative or decreasing trends. Each substance was tested individually; adjustments to alpha to protect against type I error were moot given the level of significance. All substances demonstrated a statistically significant change in the proportion of responders, except for cinnamic aldehyde ($P = 0.21$) (Table 1). Details of this technique are provided by Agresti (9). Schnuch et al. (10) utilized the Cochran-Armitage trend test for similar analyses.

The patients were patch tested in a standardized manner as outlined previously (1–8), using Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster Aksjeselskap, Venesja, Norway) applied to the back. Allergens were purchased from Hermal Pharmaceutical Laboratories, Inc. (Delmar, NY, USA) or Chemotechnique Diagnostics AB (Malmo, Sweden). The patches remained in place for 2–3 D and read at 3–7 D after placement. Patch test reactions were interpreted to be a 1+, 2+, or 3+ reaction manifested by erythematous papules, vesicles, or a spreading reaction with crust and ulceration (1–8).

Results

Table 1 summarizes the results of NACDG studies regarding responses to certain allergens between 1970 and 2002.

There is a gradual increase in the reaction positivity to nickel sulfate from 11% in 1970 to 16.9% in 2002 ($P < 0.0001$) (Fig. 1). An appreciation in the gain in response to quaternium-15 is manifested by a 2.6% response in 1976 to a peak of 9.3% in 2002 ($P < 0.0001$) (Fig. 1).

P-phenylenediamine, however, shows a consistent decrease in positive responses, starting at 8% in 1970 and decreasing to 4.8% in 2002 ($P < 0.0001$) (Fig. 2). Similarly, cinnamic aldehyde has a decreasing, but non-significant trend

Table 1. Allergic patch test positive reactions

Test substance	1970–1972		1972–1974		1974–1975		1975–1976		1984–1985		1985–1989		1992–1994		1994–1996		1996–1998		1998–2000		2001–2002		Statistic (z)†	Two-sided $P > z $ †
	<i>n</i> *	%	<i>n</i> *	%	<i>n</i> *	%	<i>n</i> *	%	<i>n</i> *	%	<i>n</i> *	%	<i>n</i> *	%	<i>n</i> *	%	<i>n</i> *	%	<i>n</i> *	%	<i>n</i> *	%		
Nickel sulfate 2.5%	1200	11.0	3000	11.0	1900	13.3	1500	12.4	1199	9.7	3969	10.5	3491	14.3	3108	14.3	3429	14.2	5827	16.2	4515	16.9	–10.2507	<0.0001
Neomycin 20%	1200	6.0	3000	5.9	1900	6.4	1500	5.6	1199	6.6	3983	7.2	3518	9.0	3104	11.6	3436	13.1	5822	11.5	4517	11.4	–14.5292	<0.0001
Quaternium-15 2%	<i>n/a</i>	<i>n/a</i>	<i>n/a</i>	<i>n/a</i>	<i>n/a</i>	<i>n/a</i>	1500	2.6	1199	6.7	3994	6.2	3500	9.6	3110	9.2	3436	9.0	5832	9.2	4524	9.3	–8.2286	<0.0001
<i>P</i> -phenylenediamine 1%	1200	8.0	3000	8.1	<i>n/a</i>	<i>n/a</i>	1500	6.2	1199	6.9	3986	6.4	3515	6.3	3111	6.8	3441	6.0	5831	4.9	4517	4.8	7.0956	<0.0001
Potassium dichromate 0.25%	1200	8.0	3000	8.1	1900	10.4	1500	8.4	1199	5.2	3949	2.4	3497	2.0	3106	2.0	3440	2.8	5833	5.8	4526	4.1	11.8147	<0.0001
Cinnamic aldehyde 1%	<i>n/a</i>	<i>n/a</i>	<i>n/a</i>	<i>n/a</i>	<i>n/a</i>	<i>n/a</i>	<i>n/a</i>	<i>n/a</i>	1199	5.9	3964	3.1	3528	2.7	3112	2.4	3443	2.8	4735	3.6	<i>n/a</i>	<i>n/a</i>	1.264	0.21
Thiuram mix 1%	1200	2.0	3000	4.2	1900	5.0	1500	4.2	1199	3.9	3996	5.5	3522	7.7	3115	6.8	3435	6.9	5830	4.7	4521	4.6	–3.3643	0.0008

**n*, approximate number of patients tested.

†Cochran-Armitage trend test.

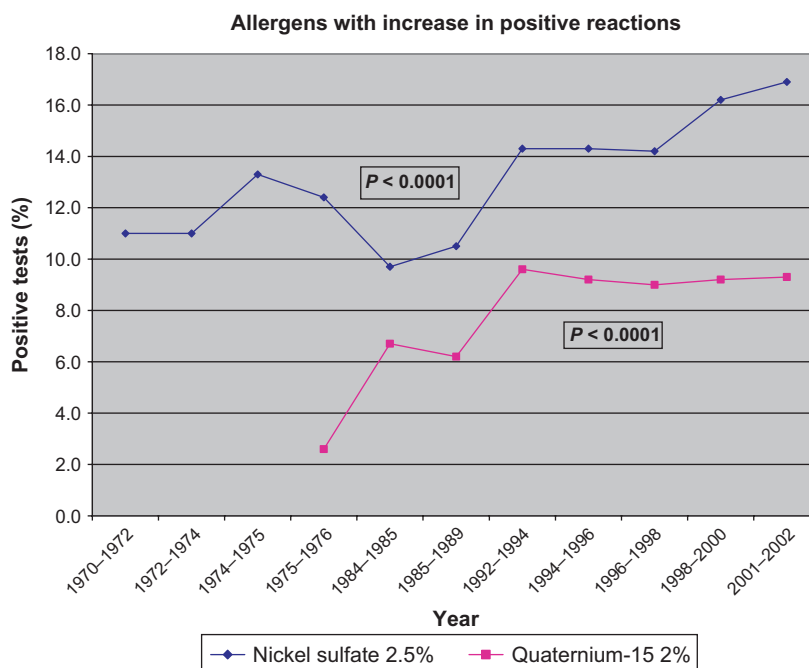


Fig. 1. Displays an increase in the reaction positivity for nickel sulfate from 11% (1970) to 16.9% (2002) ($P < 0.0001$) and an increase in response for quaternium-15 from 2.6% (1975) to 9.3% (2002) ($P < 0.0001$).

that starts out at 5.9% in 1984 and dwindles to 3.6% in 2000 ($P = 0.21$) (Fig. 2).

Although data show an initial general decrease in positive reactions for potassium dichromate, which starts with 8% positivity in 1970 and plummets to 2% in the 1992–1994 study, a recent surge in positive reactions is reflected in the high 5.8% score received in 1998–2000, which levels off at 4.1% in the 2002 studies ($P < 0.0001$) (Fig. 3).

Lastly, thiuram mix shows an increase in frequency of positive reactions from 2% in 1970 to

7.7% in 1994, but then shows a precipitous drop to 4.6% by 2002 ($P = 0.0008$) (Fig. 4). Likewise, a rise in the prevalence of response to the chemical neomycin is indicated from 6% in 1970 to 13.1% in 1998, and then drops to 11.4% in 2002 ($P < 0.0001$) (Fig. 4).

Discussion

The NACDG evaluates the prevalence of allergic reactions to chemicals in an effort to (1) make

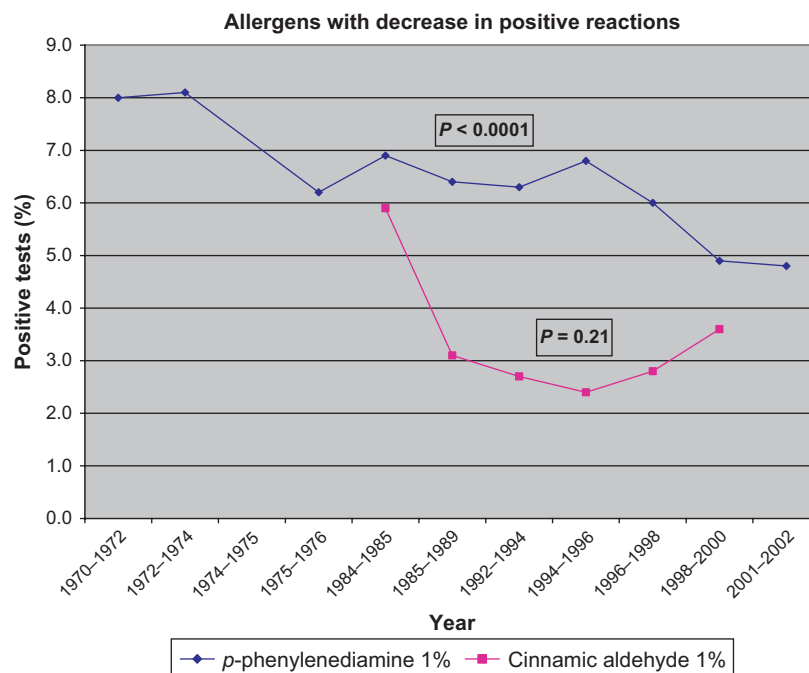


Fig. 2. Displays the decrease in reaction positivity for *p*-phenylenediamine from 8% (1970) to 4.8% (2002) ($P < 0.0001$), as well as cinnamic aldehyde, which starts out at 5.9% (1984) and dwindles to 3.6% (2000) ($P = 0.21$).

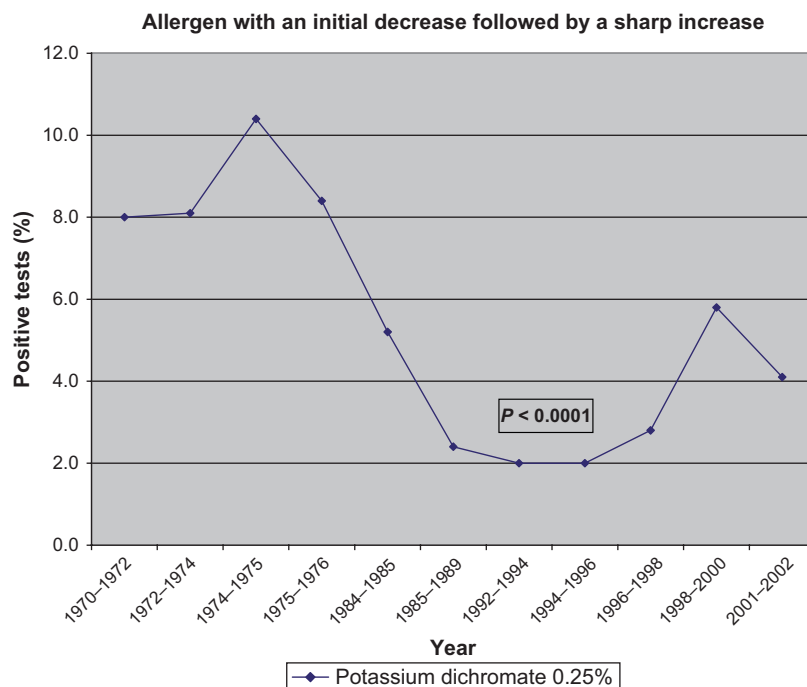


Fig. 3. Displays an initial decrease in positive reactions for potassium dichromate, which starts with 8% (1970) and decreases to 2% (1994–1996). Then increases in positive reactions to 5.8% (1998–2000) and levels off at 4.1% (2002) ($P < 0.0001$).

patch testing a current and effective means of diagnosing ACD and (2) make the trending of delayed-type contact sensitivity easily investigated. 1 way of establishing these goals is by collating multi-centre results presented in this and previous papers (1–8).

These differences are statistically significant, if the extent of the changes, as reflected in Cochran-Armitage chi-square test, $|z| \leq 0.05$. The noted substances demonstrated a statistically significant change in the proportion of responders, except for

cinnamic aldehyde (Table 1). When evaluating numerous observations over a long period, even subtle differences may be considered statistically important, but may not necessarily manifest clinical relevance. As individual patient data are not available for analysis, we could not control for potentially confounding variables such as atopic status, location, sex, and even anatomic localization in the back in a multivariable analysis. The Cochran-Armitage trend test, as well as any bivariate statistical test, only yields valid and

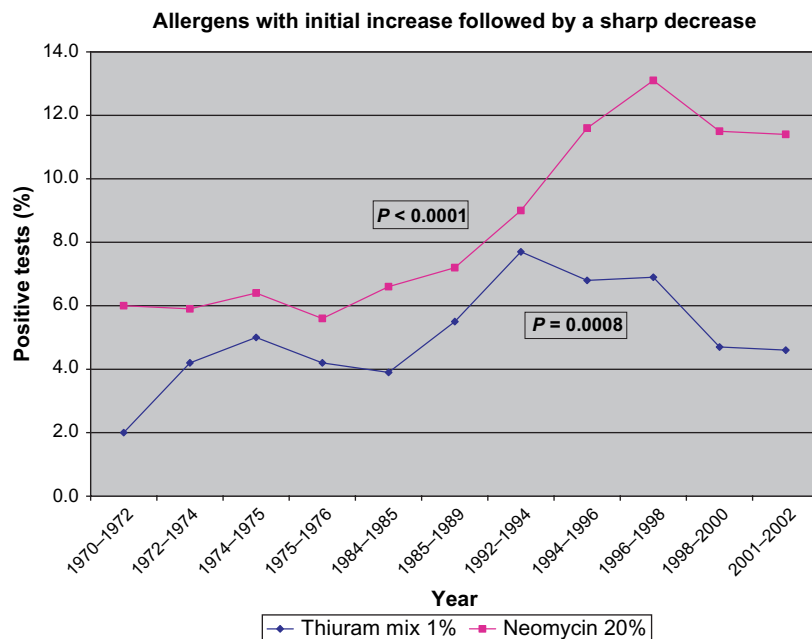


Fig. 4. Displays an increase positive reactions for thiuram mix from 2% (1970) to 7.7% (1992–1994), but then shows a drop to 4.6% (2002) ($P = 0.0008$). It also displays the rise in the response to neomycin, from 6% (1970) to 13.1% (1998), which then drops to 11.4% (2002) ($P < 0.0001$).

interpretable information if one assumes there are no other factors that could confound the examined association. Although the changes seen may demonstrate true increases or decreases in the prevalence of reactions to these test elements, we cannot rule out that the changes seen over time may actually be to changes in the confounding variables.

The statistical trend to an increased frequency in response to nickel sulfate and quaternium-15 can be explained as follows: nickel is an established causal factor in the genesis in nickel allergy (7), and as it is being used more in commercially available products, which can be reflected in social patterns such as ear piercing, this can perhaps explain the rise in reaction positivity. Quaternium-15 is found in many common household products including cosmetics, self-hygiene, and pharmaceutical products. Mainstream brands may include this chemical. The surge in reaction positivity of quaternium may be due to the increase in use of such well-known, affordable products.

P-phenylenediamine's decrease in prevalence of positive reactions to patch testing seems counter intuitive. *P*-phenylenediamine is the main ingredient found in most hair dyes. Relative to the increasing use of hair dyes due to social changes since in the last 30 years, one would expect the reaction positivity of *p*-phenylenediamine to increase not decrease.

Potassium dichromate is deemed a carcinogenic chemical. Its classification as cancerous may have led to more cautious use of the chemical and account for the decrease of reaction positivity seen in the early NACDG results.

The incidence of thiuram sensitivity appears to be decreasing with the most recent set of data. This could be the result of the greater use of vinyl and non-natural rubber latex gloves in the health-care professions.

The initial rise in the prevalence of allergic reaction to neomycin may be attributed to the fact that it was readily prescribed as a topical antibiotic by physicians during the early time periods, but the recent decline suggests that physicians may have limited their prescription regimen of this antibiotic. In a German study, a decline of the prevalence of sensitization to neomycin has been observed, which coincides with the decline of the prescription rate (11).

In an ideal and perfect world, data would be available to relate exposure to sensitization rate. Exposure includes anatomic site, disease state, and many other variables.

Our results, however, should be interpreted with caution because (1) the highly selected patients referred to the NACDG for testing and

(2) the significance of positive reactions to the patients' dermatitis incompletely documented. Also, as different suppliers (see Materials and Methods) were utilized, this must be considered an independent variable – as we have no qualitative or quantitative analytic data to confirm or deny bioequivalence (12). Despite these limitations, patch testing remains an extremely worthwhile diagnostic mechanism for the evaluation of patients with suspected ACD and these data may provide targets for public health initiative to decrease exposure.

The allergens examined statistically were chosen by visual evaluation of the data – and did not include all allergens tested during this period.

The published data largely refer to the patch test positivity. Data for clinical relevance have been added as of 1992 (5). Algorithms for determining with credibility the complex translation of patch test positivity to current clinical relevance are demanding – but important goals in future works (13, 14).

Gibbon et al. (15) (UK), showed a clear increase in frequency of thiuram allergy between 1989 and 1995 and then a decrease after 1995, which correlates with our data. Buckley et al. (16) found a decrease of cinnamic allergy between 1989 and 1996, which is also consistent with our data. However, Patel et al. (17) (UK) present data that conflict with ours. Their results indicate an increase in sensitivity to *p*-phenylenediamine at the St John's Contact Dermatitis Clinic in the United Kingdom from 1985 to 2004, while our data indicate an overall decrease in positive responses since 1970.

Similar evaluations for other sets such as from the International Contact Dermatitis Research Group, The European Environmental and Contact Dermatitis Research Group, and other regional study teams may provide insight into regional differences and perhaps offer public health options (18). Since the introduction of the nickel directive in Europe, studies (11, 19) have shown a decreasing trend in exposure to nickel and other known sensitizers, stimulating the interest of American authorities. We suspect that continuous visual and statistical monitoring of this type of data will – in the end – provide stimulus for preventive interventions. As outlined before, monitoring is well established in other parts of the world. A recent study by Wesley and Maibach (19) examined the effects of legislations that were implemented in hopes of reducing the population's exposure to known sensitizers and concluded that evidence suggests a decreasing trend of ACD of nickel, gluceryl monothioglycolate fragrances, chromate, and thiuram with the appropriate formulation changes.

Since the preparation of this manuscript, Thyssen et al. (20) has reported the 10 year prevalence of contact allergy in Denmark.

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