

Positive Patch-Test Reactions to Mixed Dialkyl Thioureas: Cross-Sectional Data from the North American Contact Dermatitis Group, 1994 to 2004

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Background: Allergic contact dermatitis from thioureas is uncommon but may result from exposure to rubber, especially neoprene.

Objectives: To (1) describe the population with positive patch-test reactions to mixed dialkyl thioureas (MDTU) (ie, diethylthiourea and dibutylthiourea); (2) determine clinical and occupational relevance associated with reactions to MDTU and identify the most commonly related sources and occupations; and (3) examine the frequency of co-reacting allergens in MDTU-positive patients.

Methods: A retrospective analysis of cross-sectional data of 22,025 patients patch-tested by the North American Contact Dermatitis Group between 1994 and 2004.

Results: Of 21,898 patients tested with MDTU, 225 (1.0%) had positive reactions; of these, 173 (76.9%) were currently relevant and 29 (17.1%) were occupationally relevant. Patients positive to MDTU were 2.6 times more likely to have foot involvement than patients with positive reactions to other allergens ($p < .0001$). Footwear was the most commonly identified source overall (20.0%) whereas gloves were the most common occupational source. Of the 173 patients with currently relevant MDTU reactions, 24.9% also reacted to another rubber allergen.

Conclusions: Current clinical relevance of reactions to MDTU was high; occupational relevance was less frequent. Patch tests with common rubber allergens (carbamates, thiurams, and mercaptobenzothiazole) may fail to detect many cases of thiourea-induced rubber allergic contact dermatitis.

THIOUREA COMPOUNDS are used as accelerators in rubber, particularly neoprene.¹ Thioureas are also used in diazo-processed papers and copy paper as antioxidants, in metal-pickling solutions as anticorrosives, and in other industrial products, including fungicides, glues, textiles, polyvinyl chloride, and insecticides.¹⁻³ Although thioureas had gained widespread use in industry by the beginning of the last century, it was not until the late 1960s that cases of allergic contact dermatitis (ACD) associated with rubber products containing thioureas were reported.³ Since then, an increasing variety of thiourea-containing rubber and nonrubber products have been reported to cause ACD.^{4,5}

While contact allergy to thioureas is now widely recognized, incidence and prevalence rates in the general population remain unknown.^{4,5} The North American Contact Dermatitis Group (NACDG), a group of 13

dermatologists in North America who collect de-identified data on patch-tested patients, began using mixed dialkyl thioureas (MDTU) consisting of diethylthiourea (DETU) and dibutylthiourea (DBTU) as part of its standard series in 1991. Since then, the prevalence of positive patch-test reactions to MDTU reported in published NACDG series from 1992 to 2004 has ranged from 0.7 to 1.3%.⁶⁻¹¹ Comfere and colleagues found that 2.4% of 1,368 patients referred for patch testing at the Mayo Clinic dermatology clinics had positive reactions to a mixture of DETU, DBTU, diphenylthiourea (DPTU), and ethylenethiourea (ETU).² In four European series, prevalence rates of sensitivity to various thiourea mixtures ranged from 0.1 to 1.2%.^{1,12-15}

Sources of thioureas can be classified as rubber (commonly neoprene) or nonrubber.⁴ Thiourea compounds documented to cause contact allergy include DETU, DBTU, DPTU, ETU, ethylbutylthiourea (EBTU), dimethylthiourea (DMTU), and thiourea (TU) (Fig 1).^{1,4} The alkyl thioureas reportedly have been used more frequently in rubber whereas reports of thiourea-induced allergy to diazo-processed paper and textile patterns have

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identified TU or DMTU as the culprit allergen.^{4,12} Reported sources of DETU or DBTU that cause ACD include neoprene-containing products such as wet suits,^{16–19} orthopedic braces and supports,^{1,4,20–25} weather stripping,²⁶ keyboard wrist supports,^{4,27,28} continuous positive airway pressure device strapping,^{4,29,30} athletic shoes and insoles,¹⁵ and swim goggles.³¹ Other reports cite rubber safety shoes,³² boots,³³ rubber manufacturing,³⁴ protective eyewear,²⁰ nylon adhesives,^{4,18} commercial paint and glue removers,^{35,36} acidic detergents,³⁷ and a phone card thermocoating as sources.³⁸

For this study, cross-sectional data from the NACDG were analyzed. Our goals were to (1) describe the population that had positive patch-test reactions to MDTU, (2) determine rates of clinical and occupational relevance associated with reactions to MDTU and identify the most commonly related sources and occupations, and (3) examine the frequency of co-reacting allergens in MDTU-allergic patients.

Methods

NACDG Database

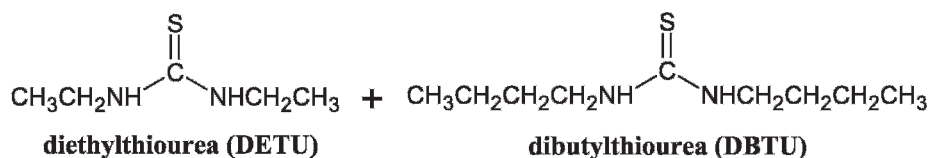
Between July 1, 1994, and December 31, 2004, 22,025 patients were patch-tested with the NACDG standard

series of 50 to 65 allergens. Information collected on patients included demographic information (age, gender, race, and atopy), sites of dermatitis (up to three sites), final diagnoses (up to three diagnoses), and occupation. Clinical relevance, occupational relevance, and source were identified for each positive reaction.

The number of allergens included in the NACDG standard series varied from 50 to 65 between 1994 and 2004. In the 1996–1998 subgroup, some individuals were tested with T.R.U.E. Test allergens (Allerderm, Phoenix, AZ) in addition to, or substituting for, NACDG standard allergens. For this analysis, a positive patch-test reaction to an NACDG standard series allergen, as part of either series used, was considered a positive reaction. The MDTU mixture used by the NACDG consisted of DETU and DBTU.

Methods for patch testing, coding, and determining final diagnoses and relevance of reactions have been previously described.¹⁰ Relevance and source codes were linked to specific allergens whereas site codes (up to three sites) and final diagnoses (up to three diagnoses) were linked to patients but not to specific allergens. For the purposes of these analyses, patch-test results coded as “definite,” “probable,” or “possible” relevance were considered currently relevant. Allergen-related source data were not collected in the 1994–1996 data set. However,

NACDG Dialkyl Thiourea Mix (MDTU)



Other Thioureas

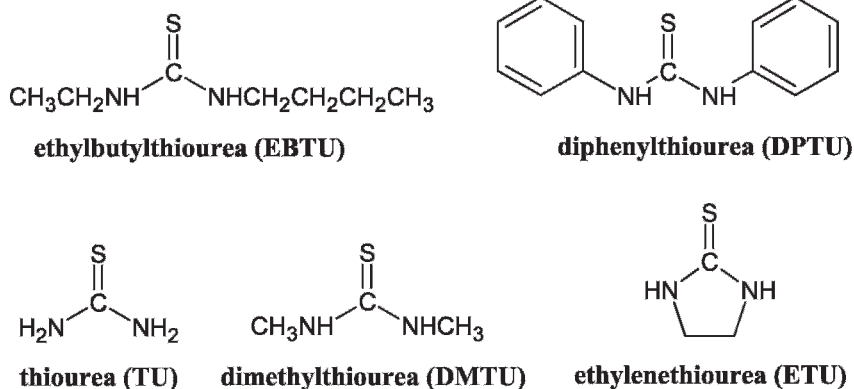


Figure 1. Thiourea compounds.

such data were subsequently collected as single-digit codes corresponding to defined categories until 2001, when a three-digit coding system was adopted. Occupation data were entered by hand in the 1994–1996 data set. In subsequent data sets, occupation was entered as a three-digit code taken from the 1990 US Department of Commerce Census Industrial and Occupational Classification Codes,³⁹ based on a standardized questionnaire. Occupational relevance data were not collected in the 1996–1998 data set. All data were manually entered into a computerized database (*Access 2003*, Microsoft Corporation, Redmond, WA) and checked for quality assurance at a central location.

Study Population and Subgroups

This analysis of de-identified data was approved by the Minneapolis Veterans Administration Medical Center's Subcommittee on Human Studies. The study focused on individuals with positive patch-test reactions to MDTU 1.0% in petrolatum. To identify patients satisfying this criterion and comparison groups, several sequential subgroups were examined (Fig 2). First, all patients patch-tested with MDTU were identified ($n = 21,898$). "Allergic" patients were defined as those patients tested with MDTU who had at least one positive patch-test reaction to any NACDG standard series allergen ($n = 15,141$); this group excluded patients who had negative, doubtful (macular erythema), or irritant reactions. This "allergic" group ($n = 15,141$) was then divided into those patients who had either a positive (group A, $n = 225$) or a negative (group B, $n = 14,916$) reaction to MDTU.

We also performed a literature search using the term "thiourea AND contact dermatitis." Relevant articles were included in the discussion for comparison to our results,

except for the study of 23 patients with shoe dermatitis by Shackelford and Belsito⁴⁰ because these patients were also included in the NACDG data set. In addition, data from 29 of the patients with positive MDTU reactions (Group A, $n = 225$) in our study were presented at the 2006 American Contact Dermatitis Society Meeting as part of a separate study.⁴¹

Analytic Methods

Statistical Analysis System software (SAS version 8.2, SAS Institute Inc., Cary, NC) and *Access 2003* software were used for these analyses. Counts and proportions were determined for demographic and allergen-related data. Pearson chi-square tests were used to compare selected demographic data and the prevalence of positive patch-test reactions to specific allergens. The Fisher exact test (two-tailed) was used where appropriate. A two-sample *t*-test using the Satterthwaite method was used to analyze differences in average age between groups A and B. Although *p* values of $< .05$ are typically considered statistically significant, the Bonferroni method⁴² of accounting for multiple comparisons was used. Fifty-four comparisons were performed; therefore, a *p* value of $< .0009$ was considered significant.

Results

Demographics

In all patients tested with MDTU ($n = 21,898$), the prevalence of positive patch-test reactions to MDTU was 1.0%. Table 1 summarizes data from each 2-year data set. Demographic information from the NACDG data set as a whole as well as from groups A and B was examined

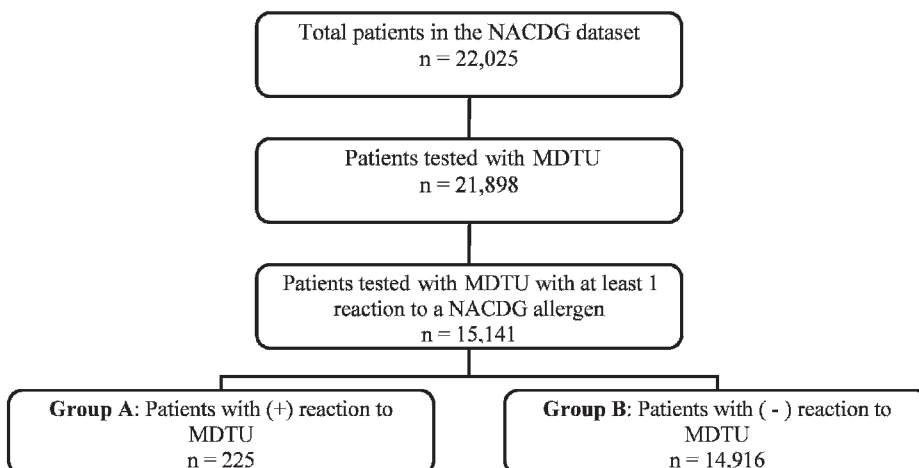


Figure 2. North American Contact Dermatitis Group (NACDG) study population and subgroups. (MDTU = mixed dialkyl thioureas; *n* = sample size)

(Table 2). MDTU-positive patients (group A) were 1.7 times more likely to be male than were “allergic” MDTU-negative patients (group B) ($p < .0001$). There were no significant differences in the distributions of race or atopy between MDTU-positive (group A) and “allergic” MDTU-negative (group B) patients.

Dermatitis Site and Final Diagnosis Codes

The prevalence rates of the ten most common site codes and the six most frequent final diagnoses are listed in Table 3 and Table 4, respectively, for MDTU-positive (group A) and “allergic” MDTU-negative (group B) patients. MDTU-positive patients (group A) were 2.6 times more likely to have foot dermatitis than were “allergic” MDTU-negative patients (group B) ($p < .0001$ for both comparisons). ACD was the most common diagnosis in both groups but was 1.2 times more likely in MDTU-positive patients than in “allergic” MDTU-negative patients ($p < .0001$). Dermatitis site and final diagnosis data, however, were linked to patients rather than to specific allergens. Therefore, to increase specificity, these data were also examined in patients with positive reactions to MDTU only (no other positive antigens). Results were similar for all patients with positive MDTU reactions (group A, data not shown).

MDTU Relevance and Source

Clinical and occupational relevance data for MDTU-positive patients (group A) are presented in Table 5. Patient occupation data for occupationally relevant reac-

tions and MDTU source data for currently relevant and occupationally relevant reactions are presented in Table 6 and Table 7, respectively. Of the 225 positive patch-test reactions to MDTU in the NACDG data set, 173 (76.9%) were currently relevant. Of the 170 positive patch-test reactions to MDTU for which occupational relevance was determined, 29 (17.1%) were occupationally relevant. The coded occupations of the 29 patients with occupationally relevant MDTU reactions were examined. The most common occupational groups were “health technologists and technicians” (11.1%) and “machine operators, assorted materials” (11.1%). For the 173 MDTU-positive patients with currently relevant reactions, the most common three-digit source codes (2001 to 2004) were those for “shoes, boots, sandals, slippers” (20.0%); “medical and miscellaneous health devices” (18.6%); and “gloves” (12.9%). The most common one-digit source codes were those for “other” (37.7%), “shoes/clothing” (34.0%), “unknown” (20.8%), and “gloves” (7.5%) from 1998 to 2000 and “other” (60.5%), “occupational” (21.1%), “unknown” (13.2%), “medications” (2.6%), and “medications + cosmetics” (2.6%) from 1996 to 1998. “Gloves” were the most common source of occupationally relevant reactions.

Cosensitization in Patients with Positive Reactions to MDTU

The prevalence rates of cosensitization to NACDG standard series allergens in MDTU-positive patients (group A) and the corresponding prevalence rates for “allergic” MDTU-negative patients (group B) are pre-

Table 1. Distribution of Patients by 2-Year Data Collection Period

Data Set				Group A [†]			Group B [‡]		
	Patients		“Allergic” Patients* (n)	Percentage		Percentage of “Allergic” Patients (%)	Percentage		Percentage of “Allergic” Patients (%)
	Patients in Each Data Set (n)	Patch- Tested with MDTU (n)		n	MDTU (%)		n	MDTU (%)	
1994–1996	2,035	2,005	1,366	16	0.8	1.2	1,350	67.3	98.8
1996–1998	4,094	4,051	2,897	55	1.4	1.9	2,842	70.2	98.1
1998–2000	5,835	5,803	4,074	64	1.1	1.6	4,010	69.1	98.4
2001–2002	4,913	4,898	3,386	38	0.8	1.1	3,348	68.4	98.9
2003–2004	5,148	5,141	3,418	52	1.0	1.5	3,366	65.5	98.5
Total	22,025	21,898	15,141	225	1.0	1.5	14,916	68.1	98.5

n = sample size; MDTU = mixed dialkyl thioureas.

*Tested with MDTU and with ≥ 1 positive patch-test reaction to any North American Contact Dermatitis Group (NACDG) allergen.

[†]Patients with a positive patch-test reaction to MDTU 1% in petrolatum (pet).

[‡]Patients with a positive patch-test reaction to an NACDG standard series allergen and a negative patch-test reaction to MDTU 1% pet.

Table 2. Demographic Data for Group A and Group B Patients

Demographic Data	NACDG Data Set (n = 22,025)		Group A* (n = 225)		Group B† (n = 14,916)		Group A vs Group B (Chi-Square, p Value)‡ (Risk Ratio [95% CI])
Age							
Mean age in years (SD)	47.5 (16.4)		45.9 (14.7)		48.1 (16.1)		.03
Range in years	< 1–97		10–87		< 1–97		—
	No.	%	No.	%	No.	%	
Gender							
Male	7,830	35.6	126	56.0	4,956	33.2	< .0001 1.69 (1.50–1.90)
Race							
White	19,157	87.0	194	86.2	13,014	87.2	.6470 0.99 (0.94–1.04)
Black	1,726	7.8	23	10.2	1,125	7.5	.1317 1.36 (0.92–2.00)
Other	1,142	5.2	8	3.6	777	5.2	.2668 0.68 (0.34–1.35)
Atopy							
Atopic§	8,064	36.6	89	39.6	5,408	36.3	.3070 1.09 (0.93–1.28)

n = sample size; NACDG = North American Contact Dermatitis Group.

*Patients with a positive patch-test reaction to mixed dialkyl thioureas 1% in petrolatum (pet).

†Patients with a positive patch-test reaction to an NACDG standard series allergen and a negative patch-test reaction to mixed dialkyl thioureas 1% pet.

‡All tests were Pearson chi-square tests with one degree of freedom, except for comparison of average age, for which a two-sample *t*-test using the Satterthwaite method was performed. Bonferroni correction for multiple comparisons was applied; $p \leq .0009$ was considered significant.

§Patients with asthma, hay fever, and/or eczema.

sented in Table 8. The likelihood of having at least one co-reaction was 4.2 times greater in MDTU-positive patients (group A, 80.9%) than in “allergic” MDTU-negative patients (group B, 19.3%) ($p < .0001$). Patients with positive reactions to MDTU (group A) were significantly more likely to have positive patch-test reactions to thiuram mix, carba mix, mercaptobenzothiazole, and mercapto mix than were “allergic” MDTU-negative patients (group B) (p values all $\leq .0007$). In patients with currently relevant MDTU reactions, the prevalence of cosensitization to any rubber allergen in the NACDG standard series was 24.9%. The prevalence of sensitization to *p*-tert-butylphenol formaldehyde resin (commonly found in neoprene adhesives)⁴³ was also almost twice as common in MDTU-positive patients (group A, 5.3%) when compared to “allergic” MDTU-negative patients (group B, 2.8%), but these data did not meet our criteria for statistical significance.

Discussion

This retrospective study of MDTU reactions recorded in a decade of NACDG data documents several key findings. Men were significantly more likely to be sensitized to

MDTU than to other NACDG allergens. Clinical relevance was high; positive patch-test reactions to MDTU were currently relevant in 173 patients (76.9%) whereas only 29 reactions (17.1%) were occupationally relevant. The foot was 2.6 times more likely to be involved in patients with a reaction to MDTU than in “allergic” MDTU-negative patients ($p < .0001$). After three-digit source codes were implemented in 2000, “shoes, boots, sandals, slippers” (20.0%), “medical and miscellaneous health devices” (18.6%), and “gloves” (12.9%) were the most commonly identified sources of currently relevant reactions to MDTU. In the 173 patients with currently relevant MDTU reactions, almost 25% had positive reactions to another rubber allergen. Finally, the prevalence rates of reactions to several common rubber allergens were significantly higher in MDTU-positive patients (group A) than in “allergic” MDTU-negative patients (group B).

There are several important points to consider when comparing the prevalence of MDTU allergy in our study (1.0%) to the prevalence of thiourea allergy reported in other studies (0.1 to 2.4%).^{1,2,6–15} First, previous studies used different thiourea mixes (such as DBTU, DETU, DPTU, and ETU)² whereas the NACDG standard dialkyl thiourea mix consists of only DETU and DBTU. Second,

Table 3. Dermatitis Sites for Group A and Group B Patients

Dermatitis Site	Group A* (n = 225)		Group B† (n = 14,916)		Group A vs Group B (Chi-Square, p Value)‡ (Risk Ratio [(95% CI)])
	No.	%	No.	%	
Hand	92	40.9	4,896	32.8	.0106 1.25 (1.06–1.46)
Scattered, generalized	52	23.1	2,727	18.3	.0633 1.26 (0.99–1.61)
Foot	46	20.4	1,163	7.8	< .0001* 2.62 (2.01–3.41)
Arm	36	16.0	2,388	16.0	.9969 1.00 (0.74–1.35)
Leg	35	15.6	1,562	10.5	.0137 1.49 (1.09–2.02)
Face	30	13.3	3,308	22.2	.0015 0.60 (0.43–0.84)
Trunk	22	9.8	1,611	10.8	.6235 0.91 (0.61–1.35)
Eyelids	6	2.7	1,147	7.7	.0048 0.35 (0.16–0.77)
Neck	6	2.7	1,300	8.7	.0013 0.31 (0.14–0.67)
Other sites§	21	9.3	2,937	19.7	.0001* 0.47 (0.32–0.71)

n = sample size.

*Patients with a positive patch-test reaction to mixed dialkyl thioureas 1% in petrolatum (pet).

†Patients with a positive patch-test reaction to a North American Contact Dermatitis Group standard series allergen and a negative patch-test reaction to mixed dialkyl thioureas 1% pet.

‡All tests were Pearson chi-square tests with one degree of freedom. Bonferroni correction for multiple comparisons was applied; $p \leq .0009$ was considered significant.

§Includes scalp, ears, anal and genital areas, eyes, areas only under clothing, lips, most exposed areas, nose, and erythroderma.

there is likely to be little cross-reactivity of alkylated thioureas within this group and other thiourea compounds.⁴³ Third, as McCleskey and Swerlick reported in their review of thiourea-induced ACD,⁴ testing with only MDTU (containing DETU and DBTU) rather than with a complete panel of thiourea allergens is likely to lead to underestimation of the true prevalence of ACD from thioureas and may miss 25% of thiourea-induced rubber ACD. Of their 37 patients with nonrubber thiourea-induced ACD, only 5 cases were due to DETU or DBTU whereas 31 cases were due to DPTU⁴; therefore, testing with the NACDG mix would have missed 84% of nonrubber thiourea-induced ACD in that group of patients.

Much of the available literature on contact allergy to thioureas is in the form of case reports and, as such, does not lend itself to the description of demographic characteristics. Furthermore, in the few studies that have

had numerous patients with thiourea allergy, no formal analyses were presented. In our study, patients with positive reactions to MDTU (group A) were slightly younger on average and were significantly more likely to be male ($p < .0001$) than were “allergic” MDTU-negative patients (group B). The distribution of gender within the group of patients who had MDTU reactions (group A), however, was approximately equal, in contrast to the general “allergic” population, which was predominately female. This may reflect the fact that the most common sources of MDTU exposure found in our study (footwear, medical devices, and gloves) are used by both genders whereas many of the other allergens in the NACDG standard series, such as those found in cosmetics and personal care products, are used more frequently by females.

Most of the previously published sources of exposure to the components of MDTU were neoprene or neoprene-

Table 4. Top Six Final Diagnoses for Group A and Group B Patients

<i>Final Diagnosis</i>	<i>Group A*</i> (n = 225)		<i>Group B†</i> (n = 14,916)		<i>Group A vs Group B (Chi-square, p Value)‡ (Risk Ratio [95% CI])</i>
	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	
Allergic contact dermatitis	199	88.4	11,317	75.9	< .0001* 1.17 (1.11–1.22)
Irritant dermatitis	37	16.4	3,021	20.3	.1578 0.81 (0.00–1.09)
Atopic dermatitis	24	10.7	1,505	10.1	.7756 1.06 (0.72–1.55)
Other dermatitis	14	6.2	1,746	11.7	.0109 0.53 (0.32–0.88)
Other dermatoses	14	6.2	1,302	8.7	.1853 0.71 (0.43–1.19)
Psoriasis	7	3.1	437	2.9	.8728 1.06 (0.51–2.21)
All other diagnoses [§]	6	2.7	1,038	7.0	.0117 0.38 (0.17–0.85)

n = sample size.

*Patients with a positive patch-test reaction to mixed dialkyl thioureas 1% in petrolatum (pet).

†Patients with a positive patch-test reaction to a North American Contact Dermatitis Group standard series allergen and a negative patch-test reaction to mixed dialkyl thioureas 1% pet.

‡All tests were Pearson chi-square tests with one degree of freedom. Bonferroni correction for multiple comparisons was applied; *p* ≤ .0009 was considered significant.

§Includes stasis dermatitis, nummular eczema, photodermatitis, seborrheic dermatitis, pompholyx, and contact urticaria.

containing products.⁴ However, no previously reported data detail the proportions of these various sources in a large cohort of patients with MDTU allergy. Not surprisingly, our analysis showed that the most common sources of MDTU exposure were products likely to contain neoprene or other rubbers. Additionally, nonrubber sources of thioureas (such as copy paper and chemicals), which have been less frequently associated with DETU or DBTU allergy in case reports,⁴ were less common in our analysis. In our analysis, “shoes, boots, sandals, slippers” and “medical and misc. health devices” were the most common sources related to MDTU reactions and accounted for almost 40% of reported sources after the implementation of three-digit source codes. The frequency of footwear as a source of exposure to MDTU likely explains the significantly increased prevalence of foot dermatitis in patients with MDTU allergy observed in our study.

Of note, “gloves” was the listed source in 12.9% and 7.5% of patients with MDTU allergy from 2001 to 2004 and from 1998 to 2000, respectively. Geier and colleagues reported that of 1,436 German patients with occupational contact dermatitis and suspected glove allergy, 0.1% had positive reactions to DBTU whereas 0.3% of 1,443 had

positive reactions to DPTU.⁴⁴ Previous case reports cited DPTU as a sensitizer in neoprene and rubber gloves.^{1,45} DETU and DBTU sensitization was described in the case reports of two patients who used rubber gloves, but relevance was not established.¹⁴ Our findings, however, suggest that gloves may be a significant source of exposure to MDTU.

The clinical relevance of thiourea contact allergy was recently studied by Comfere and colleagues. Among patients with allergy to a mixture of DETU, DBTU, DPTU, and ETU in their North American cohort (*n* = 33), 14 reactions (42%) were classified as clinically relevant.² In our analysis of 225 patients with MDTU allergy (with clinical relevance criteria similar to those used by Comfere and colleagues)² 173 reactions (76.9%) were classified as currently relevant.

The proportion of occupationally relevant reactions to MDTU has not previously been reported. In their study, Comfere and colleagues reported that many exposures were occupational, but the exact proportions of occupationally relevant reactions were not reported.² In our analysis of 170 positive reactions to MDTU for which occupational relevance data were collected, only 29 (17.1%) were occupationally relevant. The coded occupa-

Table 5. Clinical and Occupational Relevance of Positive Reactions to Mixed Dialkyl Thioureas.

Relevance	Positive MDTU Reactions (Group A)* (n = 225)	
	No.	%
Clinical		
Current (definite, probable, possible) [†]	173	76.9
Past	12	5.3
Unknown	37	16.4
Not applicable	3	1.3
Occupational [‡]		
Yes	29	17.1
Unsure	7	4.1
No	133	78.2

n = sample size; MDTU = mixed dialkyl thioureas.

*Patients with a positive patch-test reaction to MDTU 1% in petrolatum.

[†]Current relevance was considered to be a patch-test reaction coded as of definite, probable, or possible relevance.

[‡]Denominator for occupational relevance percentages was adjusted to reflect the exclusion of occupational relevance data from the data set for 1996 to 1998.

tions of patients who had occupationally relevant reactions were examined, but because of the small number of patients with a valid occupation code and the large variety of occupation codes, meaningful data were difficult to extract.

Co-reactions in patients with contact allergy to MDTU have not previously been explored in detail. Comfere and colleagues presented data on cosensitization to common rubber allergens in their patients who had clinically relevant reactions and found that approximately half of their patients also reacted to other rubber chemicals.² In our study, only 24.9% of patients who had currently relevant reactions were cosensitized to other rubber allergens. Additionally (although not statistically significant by our criteria), a higher prevalence of sensitization to p-tert-butylphenol formaldehyde resin, which is often found in neoprene adhesives⁴³ commonly used in shoes, was found in our MDTU-positive patients, suggesting increased exposure to neoprene in this population.

The production of most grades of neoprene requires a vulcanization accelerator; thioureas are used most commonly for this purpose.⁴⁶ A wide range of other accelerators may be used, however, including dithiocarbamates, thiurams, and guanidines.⁴⁶ Other allergens commonly found in general-purpose-grade neoprene include n-dodecyl mercaptan and aromatic amines, but thioureas have been the responsible allergens in the majority of reported cases of neoprene-induced ACD.⁴³ We found that cosensitization to common rubber allergens in patients with clinically relevant MDTU reactions was common but was only half as common as in patients with clinically relevant reactions to a mixture of DBTU, DETU, DPTU,

and ETU as reported by Comfere and colleagues.² This may reflect different use patterns of the components of MDTU (DETU and DBTU) as compared to the additional thioureas tested by Comfere et al. (DPTU and ETU) in the production of various grades of neoprene, but little information on the specific applications of these chemicals is available. Regardless, the relatively low prevalence of cosensitization to other rubber allergens in our study indicates that relying on tests with other more common rubber allergens alone to detect rubber allergy will fail to detect many cases of thiourea-induced rubber ACD.²

This study has several limitations. First, the data is cross-sectional; consequently, causal relationships cannot be determined. Second, a relatively small number of patients had contact allergy to MDTU, thereby limiting the power to detect statistically significant associations. Third, an even smaller number of patients had allergy only to MDTU; our examination of patient-linked data (including dermatitis site and final diagnosis) in relation to a specific allergen (MDTU) should be interpreted with this in mind. Finally, allergen-related source data are limited by both the coding physician's knowledge of products containing MDTU and the specificity of the three-digit coding system.

Conclusion

We found that 1.0% of patients who were patch-tested with mixed dialkyl thioureas (MDTU) between 1994 and 2004 had positive reactions. Positive patch-test reactions to MDTU in this population were predominately clinically relevant but were less often occupationally relevant. Sensitization to common rubber allergens in MDTU-

Table 6. Occupations of Patients with Occupationally Relevant Positive Reactions to Mixed Dialkyl Thioureas

<i>Occupational Subgroup and Specific Occupation (n)</i>	<i>Occupationally Relevant MDTU Reactions*</i> (n = 27)	
	<i>No.</i>	<i>%</i>
Health technologists and technicians	3	11.1
Dental hygienists (2)		
Health technologists and technicians (1)		
Machine operators, assorted materials	3	11.1
Painting and paint-spraying-machine operators (1)		
Photographic process machine operator (1)		
Miscellaneous machine operators (1)		
Construction trade workers (except supervisors)	2	7.4
Carpenters (1)		
Electricians (1)		
Precision workers, assorted materials	2	7.4
Electrical and electronic equipment assemblers (1)		
Miscellaneous precision workers (1)		
Mathematical and computer scientists	1	3.7
Computer systems analysts and scientists (1)		
Health assessment and treating occupations	1	3.7
Registered nurses (1)		
Mail and message distribution workers	1	3.7
Postal clerks (except mail carriers) (1)		
Material recording, scheduling, and distributing clerks	1	3.7
Stock and inventory clerks (1)		
Adjusters and investigators	1	3.7
Investigators and adjusters (except insurance) (1)		
Police and detectives	1	3.7
Police and detectives; public service workers (1)		
Food preparation and service workers	1	3.7
Waiters and waitresses (1)		
Personal service workers	1	3.7
Amusement and recreation facilities attendants (1)		
Related agricultural workers	1	3.7
Agricultural product graders and sorters (1)		
Vehicle and mobile equipment mechanics and repairers	1	3.7
Automobile body repairers and related repairers (1)		
Fabricators, assemblers, and handworkers	1	3.7
Assemblers (1)		
Factory workers [†]	1	3.7
Students [†]	1	3.7
Retired persons [†]	1	3.7
Attorneys [†]	1	3.7
Nurse aides [†]	1	3.7
Health aides [†]	1	3.7

MDTU = mixed dialkyl thioureas; n = sample size.

*Two records indicating occupationally relevant positive patch-test reactions to MDTU were omitted owing to invalid or omitted occupation codes.

[†]Hand-entered (noncoded) data from 1994 to 1996.

Table 7. Sources of Mixed Dialkyl Thioureas

MDTU Source	Sources in Group A Patients with Currently Relevant Reactions* ($n_1 = 70$; $n_2 = 53$; $n_3 = 38$) [†]		Sources in Group A Patients with Occupationally Relevant Reactions [‡] ($n_1 = 14$; $n_2 = 9$) [§]	
	No.	%	No.	%
Three-digit source codes (2001–2004)				
Shoes, boots, sandals, slippers	14	20.0	1	7.1
Medical and misc. health devices	13	18.6	2	14.3
Gloves	9	12.9	3	21.4
Clothing	4	5.7	0	0
Clothing, wearing apparel, protective equip., textiles (not otherwise specified)	4	5.7	0	0
Vehicles (air, rail, road, water)	3	4.3	0	0
Undergarments, swimwear	3	4.3	1	7.1
Safety equip., misc. (eg, masks, respirators)	3	4.3	1	7.1
Unknown	2	2.9	0	0
Not applicable	2	2.9	0	0
Antibiotics	2	2.9	0	0
Misc. health aids	2	2.9	0	0
Coatings, adhesives, dyes, inks, photographic and copying chemicals	1	1.4	1	7.1
Lubricating oils and greases	1	1.4	1	7.1
Vinyl chloride, PVC	1	1.4	1	7.1
Audio and video equip.	1	1.4	1	7.1
Cosmetics, beauty preparations, skin and health care products	1	1.4	0	0
Makeup	1	1.4	0	0
Socks, stockings, hose, nylons	1	1.4	0	0
Textiles and fabrics	1	1.4	1	7.1
No elsewhere classified	1	1.4	1	7.1
One-digit source codes (1998–2000)				
Other	20	37.7	3	33.3
Shoes and clothing	18	34.0	1	11.1
Unknown	11	20.8	2	22.2
Gloves	4	7.5	3	33.3
One-digit source codes (1996–1998)			n/a	n/a
Other	23	60.5		
Occupational	8	21.1		
Unknown	5	13.2		
Medications	1	2.6		
Medications + cosmetics	1	2.6		

equip. = equipment; MDTU = mixed dialkyl thioureas; misc. = miscellaneous; n = sample size; n/a = not available; PVC = polyvinyl chloride.

*Patients with a currently relevant positive patch-test reaction to MDTU 1% in petrolatum (pet).

[†] n_1 = total number of three-digit source codes (2001–2004); n_2 = total number of one-digit source codes (1998–2000); n_3 = total number of one-digit source codes (1996–1998). Source data were not collected in the 1994–1996 data set.

[‡]Patients with an “occupationally relevant” positive patch-test reaction to MDTU 1% pet.

[§] n_1 = total number of three-digit source codes (2001–2004); n_2 = total number of one-digit source codes (1998–2000). Source data were not collected in the 1994–1996 data set, and occupational relevance was not assessed in the 1996–1998 data set.

^{||}Percentages are calculated to reflect the proportion of listed sources in each coding system.

positive patients was statistically significantly higher than in “allergic” MDTU-negative patients but was less common than might be expected based on previous

reports. This underscores the importance of testing with thioureas in cases of suspected rubber (and especially neoprene) allergic contact dermatitis (ACD).² Future

Table 8. Frequency of Positive Patch-Test Reactions to the Top 10 Most Frequent North American Contact Dermatitis Group Standard Series Allergens and Standard Rubber Allergens

	Group A* (n = 225)		Group B† (n = 14,916)		Group A vs Group B (Chi-Square, p Value) [§] (Risk Ratio [95% CI])
	No.	%‡	No.	%‡	
Participants with > 1 positive reaction	182	80.9	2,873	19.3	< .0001* 4.20 (3.91–4.51)
Common allergens					
Neomycin sulfate 20% pet	46	20.4	2,470	16.6	.1248 1.23 (0.95–1.60)
Nickel sulfate 2.5% pet	43	19.1	3,584	24.1	.0818 0.79 (0.61–1.04)
Bacitracin 20% pet	39	17.4	1,828	12.3	.0199 1.42 (1.06–1.90)
Fragrance mix 8% pet	31	13.9	2,387	16.0	.3924 0.87 (0.62–1.21)
Thimerosal 0.1% pet	22	12.8	1,770	15.4	.3530 0.83 (0.56–1.23)
Balsam of Peru 25% pet	27	12.0	2,461	16.5	.0698 0.73 (0.51–1.04)
Quaternium-15 2% pet	25	11.1	1,974	13.2	.3473 0.84 (0.58–1.22)
Formaldehyde 1% aq	23	10.2	1,937	13.0	.2187 0.79 (0.53–1.16)
p-tert-Butylphenol formaldehyde resin 1% pet	12	5.3	417	2.8	.0229 1.91 (1.09–3.33)
Rubber allergens					
Thiuram mix 1% pet	33	14.7	1,110	7.5	< .0001* 1.97 (1.43–2.71)
Carba mix 3% pet	31	13.8	1,106	7.4	.0003* 1.86 (1.33–2.59)
Mercaptobenzothiazole 1% pet	13	5.8	335	2.2	.0005* 2.57 (1.50–4.40)
Mercapto mix 1% pet	11	4.9	270	1.8	.0007* 2.70 (1.50–4.86)
Black rubber mix 0.6% pet/IPPD 0.1% pet [¶]	4	1.8	272	1.8	1.0000 [#] 0.97 (0.37–2.59)

aq = aqueous; IPPD = N-isopropyl-N'-phenyl-4-phenylenediamine; MDTU = mixed dialkyl thioureas; n = sample size; pet = petrolatum.

*Patients with a positive patch-test reaction to MDTU 1% pet.

†Patients with a positive patch-test reaction to a North American Contact Dermatitis Group (NACDG) standard series allergen and a negative patch-test reaction to MDTU 1% pet.

‡Denominator used for all percentages was the number of completed patch-test reactions to the given allergen within the specified group.

§All tests were Pearson chi-square tests with one degree of freedom (except that notated with a # sign, which was a Fisher exact test). Bonferroni correction for multiple comparisons was applied; $p \leq .0009$ was considered significant.

||Patients with a positive patch-test reaction to MDTU and ≥ 1 other NACDG standard series allergen (group D).

¶Black rubber mix 0.6% pet was used for patch testing in the 1994–1996, 1996–1998, and 2003–2004 data sets whereas IPPD 0.1% pet was used for the 1998–2000 and 2001–2002 data sets.

#Fisher exact test.

studies that include a wider variety of individual thiourea compounds are needed to further characterize the epidemiology, cross-reactivity, sources, and clinical significance of ACD from thiourea compounds.

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