

Contact allergy and exposure patterns to thiurams and carbamates in consecutive patients

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Sensitization to rubber is most often due to sensitization to thiurams. Positive patch test reactions to carbamates are less frequent, and usually only diagnosed in patients with positive patch test reactions to thiurams as well. The aim of the present study was to describe the relative frequency of sensitization to thiuram mix (TH mix) and zinc diethyldithiocarbamate (ZDC) in a population where the exposure to these chemicals from rubber gloves was previously studied and considered to be of approximately the same order of magnitude. The thiuram derivatives seemed to be the most important sensitizers (frequency 2.8%) compared to ZDC (frequency 0.5%), which has been the most frequently reported sensitizer among the carbamates in rubber gloves. An interesting observation was that the probability that the patient was reacting to ZDC was strongly associated with the strength of the patch test reaction to TH mix. This observation may add a new aspect to the discussion about cross-reactivity versus concomitant sensitization of thiurams and carbamates.

Key words: allergic contact dermatitis; rubber chemicals; thiurams; carbamates; thiuram mix; zinc diethyldithiocarbamate; rubber gloves; cross sensitivity. © Munksgaard, 1996.

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Several thiuram and carbamate derivatives may be used as accelerators in the production of rubber gloves. Frequently, a combination of several of these chemicals is present in 1 product. All of these chemicals are more-or-less sensitizing (1, 2).

It has been a matter of discussion whether concomitant reactions in a patient to carbamates and thiurams are due to cross-reactivity or concomitant sensitization (1-7). In vitro experiments (8) have shown that the dimethylamine fraction of the molecule seems to be the sensitizing chemical structure in tetramethylthiuram monosulfide (TMTM). This observation may support the theory of cross-reactivity of, e.g., tetraethylthiuram disulfide (TETD) and ZDC. However, the fluctuations in the frequencies observed of sensitization to carbamates and thiurams may reflect differences in exposure and indicate concomitant, independent sensitization (1, 2, 4-6, 9-14). Animal experiments seem to demonstrate cross-reactivity between different derivatives of dithiocarbamates (15).

The aim of the present study was to describe the sensitization pattern to TH and ZDC, which is the corresponding carbamate to TETD. ZDC is also the carbamate that has been reported to cause substan-

tially more positive patch tests than other carbamates in rubber glove allergy (3). The exposure to the constituents of TH mix and ZDC from rubber gloves was considered to be at the same level, based on chemical analysis of some commonly used brands of surgical gloves marketed in Denmark during 1989-90 (16) (Table 1).

Patients and Methods

The population studied consisted of consecutive patients from the Copenhagen area, tested with the European standard series in a patch test clinic during 1991 to 1994. The patients were additionally tested with ZDC 1% pet. (TH mix and ZDC both from Hermal, Reinbeck). TH is composed of tetraethylthiuram disulfide (TETD) 0.25%, dipentamethylenedisulfide (PTD) 0.25%, tetramethylthiuram monosulfide (TMTM) 0.25% and tetramethylthiuram disulfide (TMTD) 0.25%, each in pet. (17) Finn Chambers were used for occlusion and fixed to the skin on the upper back with Scanpor tape (Norges-plaster). Exposure time was 2 days. Readings were made at days 2, 3-4 and 7 according to ICDRG recommendations (18).

Table 1. Cumulated amounts of thiurams and carbamates, respectively, determined after the extraction of rubber gloves with synthetic sweat

	Total thiuram extracted (mg)	Total carbamate extracted (mg)
1 (synthetic)	0	0
2 (synthetic)	0	0.4
3 (synthetic)	0	1.8
4 (natural rubber)	0.2	0.2
5 (natural rubber)	1.0	0.6
6 (natural rubber)	1.5	4.3
7 (natural rubber)	1.8	3.6
8 (natural rubber)	2.1	2.2
9 (natural rubber)	3.0	8.1
10 (natural rubber)	4.3	2.2

The gloves analyzed represented 5 commonly used surgical gloves and 5 household gloves. 7 of these were made from natural rubber latex. The quantitative analyses of chemicals extracted from the gloves with synthetic sweat included TETD, TMTM, TMTD and PTM, as well as the corresponding carbamates (16) (Table 1).

Results

A total of 2933 patients were tested. 85 (2.8%) had a positive reaction to TH mix, and 14 (0.5%) reacted to ZDC as well. No patients were identified with reaction to ZDC only. The patients reacting to TH mix were separated into 3 groups according to the strength of the patch test response (18): 5 patients had a +++ reaction to TH mix, 27 a ++ reaction and 53 a + reaction. The number of patients with a reaction to ZDC as well was 3, 7 and 4, respectively, in

the 3 groups. A highly significant association between the number of patients reacting to ZDC and the strength of the reaction to TH mix was thus demonstrated: (χ^2 : $p=0.003$) (Goodman-Kruskal's γ : 0.69, $p<0.01$). The results are shown in Fig 1.

Discussion

The observed frequency of thiuram sensitization (2.8%) is in accordance with the frequencies reported from other patch test clinics (4, 6, 9, 10), although higher frequencies are reported from, e.g., Spain (12.2% (5)) and Canada (5.4% (11)). The frequency of sensitization to ZDC (0.5%) seems to be slightly below the frequency reported in other studies (1, 2, 4, 5, 9, 13, 14), but similar to the frequency reported from Germany (0.8% (6)). However, most studies report the frequency of reactions to carba mix and not ZDC. The frequencies are therefore not directly comparable. The carba mix may cause irritant reactions (19) and the very high frequencies reported in some countries may partly be due to irritant reactions. No patients with positive patch test reactions to ZDC and negative reaction to TH mix were found in our study. This finding is in accordance with other studies (1, 3, 4, 6, 12).

As no major differences in the exposure to thiurams and carbamates were demonstrated in the population, we assume that the 4 thiuram derivatives studied here are important sensitizers in rubber gloves compared to their corresponding carbamates, in particular ZDC. Testing with ZDC seems currently redundant, as also claimed by Logan & White (19).

The finding that the likelihood of reacting to ZDC significantly increases with increasing strength of the patch test reaction to TH mix may indicate that cross-reactivity between thiurams and carbamates does occur. The demonstrated association might, however, also express that patients with strong reactions to thiurams may have had more severe eczema followed by a more damaged skin barrier. This damage could facilitate sensitization to carbamates.

The study was retrospective, and patch testing with zinc dimethyldithiocarbamate and penta-methylene dithiocarbamate was not carried out. According to the literature (3), however, sensitization to these carbamate derivatives seems to be rare.

ZDC-REACTIONS, ASSOCIATED TO THE DEGREE OF REACTIVITY TO TH-MIX

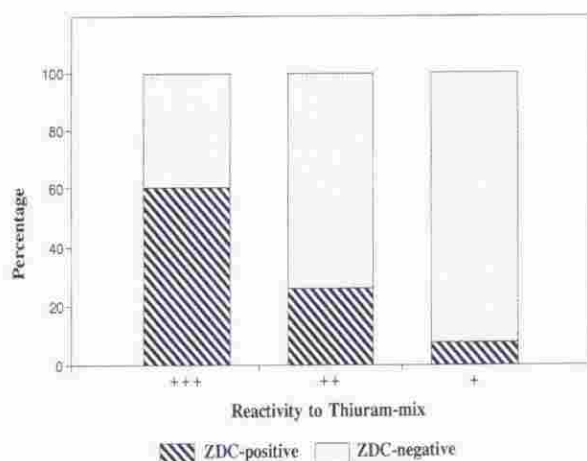


Fig. 1. % of patients reacting to TH mix 1% pet., and concomitantly reacting to ZDC 1% pet. The TH-mix-positive patients are grouped according to the strength of reaction to TH mix (18); $p=0.003$.

References

1. Cronin E. Rubber. In Cronin E (ed): *Contact dermatitis*. New York: Churchill Livingstone, 1980: 716-745.
2. Taylor J S. Rubber. In Fisher A A (ed): *Contact dermatitis*. Lea & Febiger, Philadelphia 1986: 603-647.
3. Estlander T, Jolanki R, Kanerva L. Allergic contact dermatitis from rubber and plastic gloves. In: Mellström G, Wahl-

- berg J, Maibach H (eds): *Protective gloves for occupational use*. Boca Raton: CRC, 1994: 221-240.
4. Rudzki E, Ostaszewski K, Grzywa Z, Kozłowska A. Sensitivity to some rubber additives. *Contact Dermatitis* 1976; 2: 24-27.
 5. Condé-Salazar L, Del-Río E, Guimarães D, Domingo A G. Type IV allergy to rubber additives: 10-year study of 686 cases. *JAAD* 1993; 29: 176-180.
 6. Von Hinzenstern J, Heese A, Koch H-U, Peters K-P, Hornstein O P. Frequency, spectrum and occupational relevance of type IV allergens to rubber chemicals. *Contact Dermatitis* 1991; 24: 244-252.
 7. Van Ketel WG, Van den Berg W H H W. The problem of the sensitization to dithiocarbamates in thiuram-allergic patients. *Dermatologica* 1984; 169: 70-75.
 8. Kimber I, Quirke S, Cumberbatch M, Ashby J, Paton D, Aldridge R D, Hunter J A A, Beck M H. Lymphocyte transformation and thiuram sensitization. *Contact Dermatitis* 1991; 24: 164-171.
 9. Hirano S, Yoshikawa K. Patch testing with European and American standard allergens in Japanese patients. *Contact Dermatitis* 1982; 8: 48-50.
 10. Lammintausta K, Kalimo K. Sensitivity to rubber. *Dermatosen in Beruf und Umwelt* 1985; 33: 204-208.
 11. Lynde C W, Warshawski L, Mitchell J C. Screening patch tests in 4190 eczema patients 1972-81. *Contact Dermatitis* 1982; 8: 417-421.
 12. Wilson H T H. Rubber dermatitis. *Br J Derm* 1969; 81: 175-179.
 13. Shehade S A, Beck M H, Hillier V F. Epidemiological survey of standard series patch test results and observations on day 2 and day 4 readings. *Contact Dermatitis* 1991; 24: 119-122.
 14. Doms-Goossens A. A computerized retrieval system of contact dermatitis. *Seminars Dermatol* 1986; 5: 249-254.
 15. Matsushita T, Yoshioka M, Arimatsu Y, Nomura S. Experimental study on cross contact allergy due to dithiocarbamate fungicides. *Ind Health* 1977; 15: 87-94 (abstr).
 16. Knudsen B B, Larsen E, Egsgaard H, Menné T. Release of thiurams and carbamates from rubber gloves. *Contact Dermatitis* 1993; 28: 63-69.
 17. Van Ketel W G. Thiuram-mix. *Contact Dermatitis* 1976; 2: 232-236.
 18. Wilkinson S M et al. Terminology of contact dermatitis. *Acta Dermato-Venerologica* 1970; 50: 287-292.
 19. Logan R A, White I R. Carbamix is redundant in the patch test series. *Contact Dermatitis* 1988; 18: 303-304.
 20. Heese A, Hinzenstern J, Peters K-P, Koch H-U, Hornstein O P. Allergic and irritant reactions to rubber gloves in medical health services. *JAAD* 1991; 25: 831-839.

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