

Occupational rubber glove allergy: results of the Information Network of Departments of Dermatology (IVDK), 1995–2001

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About 21% of the patients with occupational contact dermatitis registered in the Information Network of Departments of Dermatology (IVDK) in the years 1995–2001 were patch tested due to suspected rubber glove allergy. We analysed reaction frequencies to thiurams, dithiocarbamates, mercaptobenzothiazole (MBT) and its derivatives, thioureas, and 1,3-diphenylguanidine (1,3-DPG). Thiurams were by far the most frequent rubber allergens in these patients (16.2% positive reactions, age- and sex-standardized), and the reaction frequency showed a decline from 20.9% in 1997 to 12.8% in 2000. However, this trend was not statistically significant, and was followed by an increase to 16.5% in 2001. All other rubber allergens showed no time trend at all. Although, according to manufacturers' information, the use of dithiocarbamates and MBT derivatives in rubber glove production increased in recent years, these allergens elicited positive reactions in only about 3% of the patients tested, and showed no increasing trend. Thioureas and 1,3-DPG are not widely used in rubber glove production, and play only a minor role in rubber glove contact allergy. Most of the positive reactions to 1,3-DPG are probably false-positive, irritant reactions.

Key words: 1, 3-diphenylguanidine; dithiocarbamates; glove allergy; mercaptobenzothiazole derivatives; occupational contact allergy; rubber contact allergy; thioureas; thiurams. © Blackwell Munksgaard, 2003.

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Protective gloves are worn to avoid skin contact with hazardous, toxic, infectious, irritant or sensitizing materials. Because of their good fit, mostly elastomer gloves are used. Up to now, it has been impossible to produce an elastomer glove without the use of sensitizing chemicals, the most well-

known of these being vulcanization accelerators. Over recent decades, thiurams have been the most important rubber allergens, particularly in medical gloves (1–5). Surveillance of ingredient lists of medical gloves and gloves for protection against chemical hazards has shown that most interna-

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Table 1. Patients with occupational contact dermatitis and suspected glove allergy, IVDK, 1995 to 2001

Year	1995	1996	1997	1998	1999	2000	2001	Total
Count	277	326	339	341	245	315	296	2047
Male	82 (29.6%)	75 (23.0%)	108 (31.9%)	117 (34.3%)	78 (31.8%)	106 (33.7%)	109 (36.8%)	636 (31.1%)
Atopic dermatitis	51 (18.4%)	82 (25.2%)	104 (30.7%)	88 (23.8%)	70 (28.6%)	80 (25.4%)	97 (32.8%)	550 (26.9%)
Age $\geq$ 40 years	80 (28.9)	95 (29.1%)	108 (31.9%)	129 (37.8%)	105 (42.9%)	139 (44.1%)	136 (45.9%)	748 (36.5%)
Health care workers	147 (53.1%)	164 (50.3%)	154 (45.4%)	132 (38.7%)	109 (44.5%)	134 (42.5%)	108 (36.5%)	920 (44.9%)
Cleaners	23 (8.3%)	29 (8.9%)	25 (7.4%)	37 (10.9%)	15 (6.1%)	27 (8.6%)	17 (5.7%)	163 (8.0%)
Hairdressers	11 (4.0%)	14 (4.3%)	10 (2.9%)	12 (3.5%)	3 (1.2%)	15 (4.8%)	16 (5.4%)	79 (3.9%)

tional rubber glove producers replaced thiurams by dithiocarbamates and/or mercaptobenzothiazole and its derivatives in recent years (6, 7).

Probably as a consequence of decreased usage of thiurams, Gibbon *et al.* reported decreasing frequencies of sensitization to thiurams in health care workers with hand dermatitis in the UK, declining from 27% in 1994 to about 10% in 1998 (1). We analysed data of the Information Network of Departments of Dermatology (IVDK) to see if the above-mentioned changes in the use of rubber accelerators by the glove producers are mirrored by the sensitization frequencies observed in patients with occupational glove allergy.

Materials and Methods

Of the 67188 patients patch tested in the years 1995–2001 in the departments of dermatology comprising the IVDK (<http://www.ivdk.org>; 8), 9551 suffered from occupational contact dermatitis (14.2%). 3786 patients were tested due to suspected glove allergy (5.6%). Both criteria were fulfilled by 2047 patients, which is 21.4% of those with occupational contact dermatitis. The proportion of men was 31.1% ($n = 636$), ranging from 23.0% (in 1996) to 36.8% (in 2001) over the years. 550 patients (26.9%; range: 18.4% in 1995 to 32.8% in 2001) had atopic dermatitis, and 36.5% of the patients ($n = 748$) were 40 years and older (range: 28.9% in 1995 to 45.9% in 2001). 920 patients (44.9%; range 36.5% in 2001 to 50.3% in 1996) were health care workers, such as nurses, physicians, dentists, and laboratory technicians. The next most frequent occupational groups were cleaners ($n = 163$, i.e. 8.0%; range 5.7% in 2001 to 10.9% in 1998), and hairdressers ($n = 79$, i.e. 3.9%; range 1.2% in 1999 to 5.4% in 2001). None of the above-mentioned indices showed a constant increase or decrease with time (see Table 1).

Patch tests were performed according to internationally accepted guidelines and readings were documented following the recommendations of the German Contact Dermatitis Research Group

(DKG) (9, 10). Patch test substances were purchased from Hermal, Reinbek, Germany.

We analysed crude as well as age- and sex-standardized (11) proportions of positive reactions (i.e. +, ++, or +++) at day 3 (D3) to thiurams, dithiocarbamates, mercaptobenzothiazole (MBT) and its derivatives, thioureas, and 1,3-diphenylguanidine [1,3-DPG; 1% petrolatum (pet.)] using the following group definitions.

- Thiurams: positive reaction to thiuram mix 1% pet., and/or at least 1 of its constituents tetramethylthiuram monosulfide (TMTM), tetramethylthiuram disulfide (TMTD), tetraethylthiuram disulfide (TETD), and dipentamethylene-thiuram disulfide (DPTD) at 0.25% pet.
- Dithiocarbamates: positive reaction to zinc diethyldithiocarbamate (ZDEC) 1% pet. or zinc dibutyldithiocarbamate (ZDBC) 1% pet.
- MBT and its derivatives: positive reaction to MBT 2% pet., and/or mercapto mix 1% pet. or 2% pet., and/or at least 1 of the mix constituents *N*-cyclohexyl-2-benzothiazylsulfenamide (CBS) 1% pet., dibenzothiazyl disulfide (MBTS) 1% pet., and morpholinylmercaptobenzothiazole (MOR) 0.5% pet.
- Thioureas: positive reaction to diphenylthiourea and/or dibutylthiourea at 1% pet.

Statistical analysis

Statistical analysis was done using SAS 8.2. software (SAS Institute, Cary, NC, USA). Reaction frequencies were directly age- and sex-standardized to the IVDK standard population, according to population-adjusted frequency of sensitization (PAFS) (11, 12).

Results

Table 2 shows the number of patients tested with each of the rubber allergens mentioned above and

Table 2. Reactions at D3 to rubber allergens in patients with occupational contact dermatitis and suspected glove allergy, IVDK, 1995 to 2001

Allergen	No. of patients tested	% positive reactions
Thiurams (at least 1 of 1. to 5.)	1976	15.1
1. Thiuram mix	1916	12.9
2. Tetraethylthiuram disulfide (TETD)	1412	10.3
3. Tetramethylthiuram monosulfide (TMTM)	1423	8.1
4. Tetramethylthiuram disulfide (TMTD)	1420	7.1
5. Dipentamethylenethiuram disulfide (DPTD)	1424	5.1
Dithiocarbamates (at least 1 of 6. to 7.)	1987	3.4
6. Zinc diethyldithiocarbamate (ZDEC)	1987	3.3
7. Zinc dibutyldithiocarbamate (ZDBC)	1377	0.4
Mercaptobenzothiazole and its derivatives (at least 1 of 8. to 13.)	1984	2.9
8. Mercapto mix 2% pet.	106	0.0
9. Mercapto mix 1% pet.	1815	2.2
10. Mercaptobenzothiazole	1683	2.0
11. Morpholinylmercaptobenzothiazole (MOR)	1416	2.5
12. <i>N</i> -Cyclohexyl-2-benzothiazylsulfenamide (CBS)	1439	1.8
13. Dibenzothiazyl disulfide (MBTS)	1439	1.0
Thioureas (at least 1 of 14. to 15.)	1444	0.4
14. Diphenylthiourea	1443	0.3
15. Dibutylthiourea	1436	0.1
1,3-Diphenylguanidine	1455	1.9

the respective crude percentage of positive reactions at D3. Among thiurams, TETD was the leading allergen with 10.3% positive reactions. Reactions to dithiocarbamates were almost exclusively to ZDEC, while only 5 patients reacted to ZDBC. The mercapto mix 2% pet., consisting of 4 components, i.e. MBT, and its derivatives MOR, CBS, and MBTS, was replaced by the mercapto mix 1% pet., that consisted of the 3 derivatives only (without MBT), in March 1995 (13). Due to this change, only 106 patients were tested with the old mix (2% pet.). Of the MBT derivatives, MOR elicited positive reactions most frequently (2.5%), even more than MBT itself (2.0%).

Thioureas and 1,3-DPG were not routinely tested in the total study population, but only in about 1450 patients. Positive reactions to thioureas were seen in 0.5% of the patients (age- and sex-standardized; range: 0.0% to 1.0%), and to 1,3-DPG in 1.9% (age- and sex-standardized; range: 0.8% to 3.8%). Of the 28 patients testing positively to 1,3-DPG, 27 had weak positive reactions, i.e. + only. Erythematous reactions occurred in 42 patients. Thus, the reaction index (14) of 1,3-DPG was - 0.2.

Over the whole study period, thiurams remained the most frequent allergens in this group of patients with occupational rubber glove allergy, with an overall age- and sex-standardized proportion of 16.2% positive reactions. The maximum was 20.9% in 1997, the minimum 12.8% in 2000 (Fig. 1). While from 1997 to 2000 there was a constant, al-

though nonsignificant decline in thiuram reactions (Cochran–Armitage trend test, $P = 0.10$, 2-sided), the frequency of thiuram reactions rose again in 2001, amounting to 16.5%. However, comparing the nonadjusted reaction frequencies in 2000 and 2001 (12.7% and 16.3%, respectively) by Fisher's exact test revealed that the increase was not statistically significant. Positive reactions to dithiocarbamates occurred in 3.9% (age- and sex-standardized) of the patients (range over the years: 2.4% to 5.9%), with no constant trend. The latter also applies to MBT derivatives, which gave positive reactions in 3.0% (age- and sex-standardized) of the patients tested (range: 1.3% to 5.4%).

Concomitant sensitization to thiurams and dithiocarbamates occurred in 63 patients, i.e. 3.2% of the 1975 patients tested with both groups. Of these, altogether 298 reacted positively to thiurams, and 68 to dithiocarbamates. Thus, 92.7% [95% confidence interval (CI): 83.7–97.6%] of the patients reacting to dithiocarbamates also had a reaction to thiurams, and 21.1% (95% CI: 16.6–26.2%) of the individuals sensitized to thiurams also reacted positively to dithiocarbamates.

Discussion

In accordance with the results that we found in a recent study on different patch test concentration of thiurams (15), TETD was the leading allergen among this group of rubber accelerators. However, most patients with thiuram allergy react to more

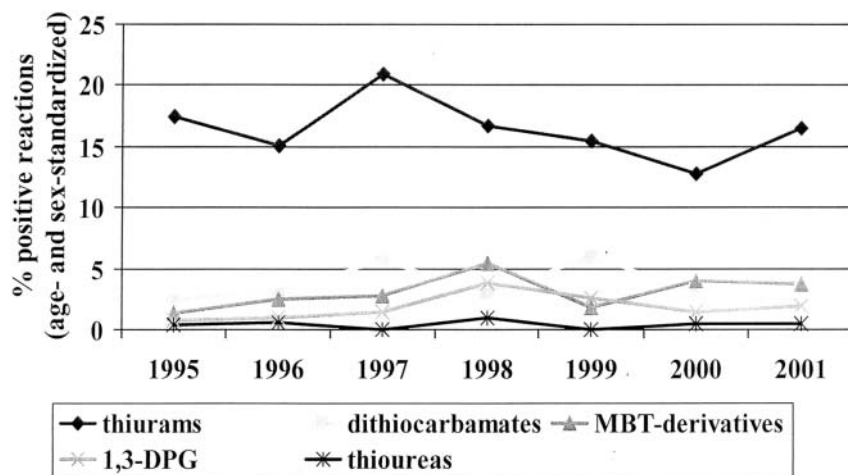


Fig 1. Sensitization to rubber allergens in patients with occupational contact dermatitis and suspected glove allergy.

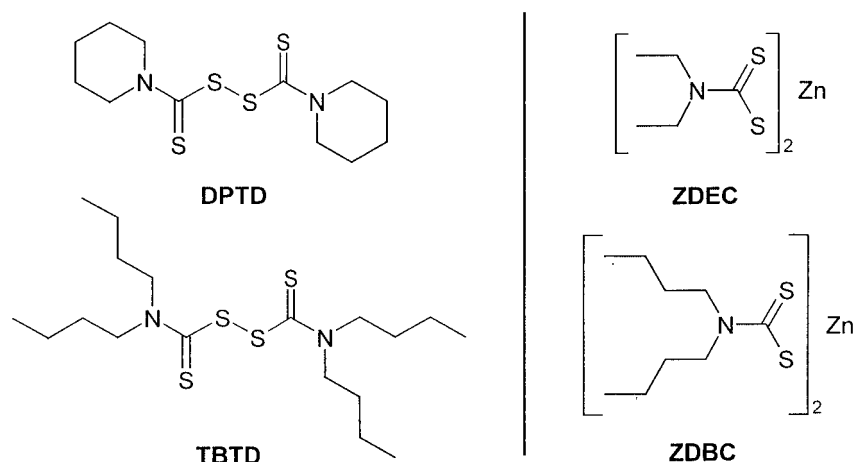


Fig 2. Chemical structures of dipentamethylenethiuram disulfide (DPTD), tetrabutylthiuram disulfide (TBTD), zinc diethyldithiocarbamate (ZDEC), and zinc dibutyldithiocarbamate (ZDBC).

than 1 thiuram only (16), and in rubber production a combination of thiurams is usually used (5). Among MBT and its derivatives, MOR elicited positive reactions most frequently. A detailed analysis of patch testing with this group of rubber allergens and a discussion of its special problems (stability, conversion of derivatives into MBT) has recently been published (13).

Thiurams still are the leading allergens in occupational rubber glove allergy. In accordance with the data published by Gibbon *et al.* (1), we saw a decline of thiuram sensitizations in the 1990s. However, while in the UK the decline was noted between 1994 and 1998, this trend was seen somewhat later in our data, from 1997 to 2000. Knowing that several international companies producing protective gloves replaced thiurams by dithiocarbamates during recent years, it was surprising to observe a rise in thiuram allergies from 2000 to 2001. Although the increase was not statistically significant, thiuram allergies in this group of patients should be observed carefully in the future. One

possible explanation for this 'broken trend' might be that in many hospitals huge amounts of cheap 'no-name' latex gloves are used, and it cannot be excluded that cheaply produced latex gloves still, or even increasingly, contain thiurams, because the production process is technically well established and thiurams are relatively cheap.

Dithiocarbamates and MBT derivatives provoked positive reactions much less often, and there was no evidence of an increase in sensitizations during recent years. This is surprising, because these vulcanization agents are now the most frequently mentioned ones in rubber glove ingredients lists. Possibly, a lesser amount of these substances is released from the glove, thus keeping the exposure low, or their sensitizing potential is indeed lower, compared to thiurams, which has previously been postulated by Knudsen and Menné regarding dithiocarbamates (17). However, recent experimental studies with the local lymph node assay (LLNA) in mice and the maximization test in guinea pigs revealed a high diversity of sensitiza-

tion potential among the various substances within both groups of chemicals, and comparable potencies have been estimated for some substances of both chemical classes, for example ZDEC and TMTD (18, 19). Against this background, our data (7.1% positive reactions to TMTD vs. 3.3% to ZDEC) might point towards more intense exposure to the thiuram, possibly due to higher release from the rubber glove.

The analysis of cross-reactions between thiurams and dithiocarbamates confirms the clinical experience that individuals sensitized to thiurams may tolerate gloves with dithiocarbamates for a certain time (before they also develop a dithiocarbamate allergy), but that patients with a contact allergy to dithiocarbamates never tolerate thiuram-containing rubber gloves (5). Due to the close chemical similarity between these 2 groups, immunological cross-reactivity is the probable reason for this phenomenon (17). Nevertheless, because these 2 groups of related chemicals often occur simultaneously in natural rubber latex, concomitant sensitization cannot be ruled out.

Finally, our results may encourage some reflections on structure-activity relationships between different rubber allergens (Fig. 2). Among the thiurams tested, DPTD caused allergic reactions least frequently, in accordance with former studies (20–22). Likewise, tetrabutylthiuram disulfide (TBTD) shows a significantly lower sensitization potential when tested in the local lymph node assay (LLNA) in mice compared to TMTD and TETD (19). With regard to the dithiocarbamates, we also found a higher frequency of sensitization to ZDEC than to ZDBC. This is in accordance with the low sensitization potential of ZDBC in the LLNA, compared to the much stronger sensitizer zinc dimethyldithiocarbamate (ZDMC) and especially ZDEC (19). Therefore, it may be concluded that thiurams as well as dithiocarbamates with a longer (bulky) chain might be less potent sensitizers in man in accordance with the lower frequency of reactions to ZDBC and (to a lesser extent) DPTD. For this reason, increased usage of such compounds might be indicated for preventive reasons.

Thioureas and 1,3-DPG seem to play only a minor role in rubber glove contact allergies. A look at rubber glove ingredient lists gives the impression that exposure to these substances is rather low, because they are not very frequently used. With 1,3-DPG, an additional diagnostic problem is its low reaction index, indicating a poor ability to distinguish between allergic and irritant reactions. As in most cases no clinical relevance for a weak positive reaction, i.e. a + reaction, to 1,3-DPG can be established, most of these reactions are probably false-positive (23).

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