Occupational contact allergy caused by rubber gloves – nothing has changed

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Summary

Background. Allergic contact dermatitis caused by rubber gloves is not infrequent, and has almost exclusively been attributed to contact sensitization to accelerators. Thiurams have been the most frequent allergens, followed by dithiocarbamates.

Objectives. To describe the current allergen pattern in patients with occupational allergic contact dermatitis caused by rubber gloves.

Methods. This study was a retrospective analysis of data from the Information Network of Departments of Dermatology (IVDK), 2002–2010.

Results. Of 93 615 patients patch tested in the IVDK, 3448 both suffered from occupational dermatitis and were tested because of suspected glove allergy. Among these, healthcare workers were the largest group (n = 1058). Of all occupational dermatitis patients, 13% were sensitized to thiurams, 3.5% to dithiocarbamates, 3% to mercaptobenzothiazole and/or its derivatives, and 0.4% to thioureas. Positive test reactions to 1,3-diphenylguanidine were seen in 3.0%. Reaction frequencies varied with the years, but showed no uniform time trend.

Conclusions. As compared with a former IVDK data analysis (1995–2001), there was no change in sensitization pattern and no decline in sensitization frequencies. This is in line with data from the literature. Particularly in healthcare, there is a need for (i) allergen declaration on the glove package, and (ii) gloves with reduced accelerator content.

Key words: contact allergy; occupational; protective gloves; rubber allergy; thiurams.

In various occupational settings, gloves are worn to protect the user from harmful substances, such as infectious agents, toxic substances, sensitzers, and detergents, or simply from prolonged exposure to water. For better handling properties, most gloves are made from elastic material, for example natural rubber latex or synthetic rubber such as nitrile rubber. In the production process of gloves made from these materials, vulcanizing agents (accelerators) are indispensable. As they are not completely used up in production, varying residual amounts of accelerators are released from the gloves during usage. Generally, sulfur-containing chemicals, such as thiurams, dithiocarbamates, and mercaptobenzothiazole (MBT) derivatives, are used as vulcanizing agents (1–4).

Accelerator-induced allergic contact dermatitis is not uncommon, and the corresponding type IV sensitization is found frequently among patients with occupational dermatitis working in the professions concerned, in particular among healthcare workers, cleaners, and hairdressers (5–7).
An analysis of data from the Information Network of Departments of Dermatology (IVDK), 1995–2001, revealed that thiurams were by far the most frequent contact allergens in this context, whereas other accelerators sensitized less frequently (7). In a logistic regression analysis of IVDK data, 1992–2006, a significant decline in the age-standardized frequency of positive patch test reactions to thiuram mix in healthcare workers over these years was shown. However, this analysis did not focus on patients with occupational dermatitis and suspected glove allergy (5). Similar findings were made at Gentofte Hospital, Copenhagen, Denmark, in 1995–2004 (8). Recently, one manufacturer presented the first accelerator-free medical glove (9). These facts prompted us to review recent IVDK data in order to detect any time trend in accelerator sensitization.

Materials and Methods

The IVDK is a network of, currently, 56 departments of dermatology in Germany, Switzerland, and Austria, dedicated to the clinical epidemiology of contact allergy. Its operating principles and quality control procedures are described in detail elsewhere (10, 11). All participants in the IVDK are members of the German Contact Dermatitis Research Group (DKG). Patch tests are performed and read according to International Contact Dermatitis Research Group (ICDRG) and DKG guidelines (12). Patch test substances are purchased from Almirall Hermal, Reinbek, Germany. Patch test results and clinical data of all patch tested patients are transferred anonymously to the IVDK central office at the University of Goettingen.

IVDK data of the years 2002–2010 form the basis of the retrospective data analysis presented in this article. We selected data of patients with suspected occupational glove-induced dermatitis. For data management and analysis, the statistical software package SAS™ 9.2 (SAS Institute, Cary, NC, USA) was used. For data analysis, patch test reactions at D3 were selected. In a few exceptional cases, when no reading was performed at D3, but a reading was performed at D4 instead, this reaction was chosen for data analysis. Positive reactions were summarized from all reactions coded as +, ++, or ++++, according to DKG definitions, that is, reactions with erythema, papules, infiltration, and (coalescent) vesicles, respectively. Proportions of positive reactions are presented with accompanying exact 95% confidence intervals (CIs). Reaction indices (RIs) and positivity ratios (PRs) were calculated as indicated in the original publications (13, 14).

Results

From 2002 to 2010, 93,615 patients were patch tested in the departments of dermatology forming the IVDK. Of these, 14,148 patients (15.1%) suffered from occupational dermatitis. Among occupational dermatitis patients, 3448 (24.4%) were tested because of suspected glove allergy, and thus constituted the study sample. A brief description of these patients is given in Table 1. As can be seen, both the age and sex distribution and the share of patients with former or current atopic dermatitis changed over the years. The proportion of men ranged from 33.7% (2003) to 46.5% (2008), the proportion of atopics ranged from 24.2% (2002) to 42.4% (2007), and the proportion of patients aged ≥40 years ranged from 44.4% (2003) to 59.5% (2009). Healthcare workers were the largest occupational group concerned (1058 patients, i.e. 30.7%) and comprised the following professions: nurses, doctors’ assistants, geriatric nurses, medical laboratory technicians, physicians, dentists, and veterinarians. Other sizeable occupational groups included cleaning personnel (262 patients; 7.6%), mechanics, machinists, and toolmakers (253 patients; 7.3%), and hairdressers (195 patients; 5.7%). Although the proportions of occupational groups varied over the years in a certain range, their ranking remained stable.

Thiuram mix (1% pet.), zinc diethyldithiocarbamate (ZDEC; 1% pet.), MBT (2% pet.), and mercapto mix (1% pet.) are part of the current DKG baseline series, and were components of the baseline series throughout the entire study period. The baseline series was patch tested in ~89% of the patients. Single constituents of the mixes and other accelerators were patch tested as part of the DKG rubber series in ~72% of the patients in our study sample. The proportions of positive reactions to these allergens in the whole study group (3448 patients) and in the healthcare worker subgroup (n = 1058) are shown in Table 2. In addition to the single patch test preparations, we also computed frequencies of reactions to different chemical groups, that is, thiurams, dithiocarbamates, MBT and its derivatives, and thioureas.

With 13.0% positive reactions, thiurams were by far the most frequent allergens. The frequency of reactions was slightly higher among healthcare workers (15.0%) than in the remaining patients (12.2%). The difference was statistically significant (p = 0.02, χ²-test).

Among dithiocarbamates, which elicited positive reactions in 3.5% of the patients, ZDEC was the most prominent allergen, and reactions to the other two dithiocarbamates were rare (0.2%). In addition, all positive reactions to zinc dibutyldithiocarbamate and zinc dibenzylidithiocarbamate were weak positive reactions (i.e. +)
only, and, in both cases, twice as many doubtful and irritant reactions occurred.

Taken together, reactions to MBT or at least one of its derivatives (3.0%) were almost as frequent as reactions to dithiocarbamates. MBT and mercapto mix were patch tested in parallel in 3057 patients. Fifty patients reacted to both test preparations, 21 reacted to MBT but not to the mix, and 14 reacted to the mix but not to MBT. Of those 100 patients reacting to MBT or at least one of its derivatives, 86 reacted to MBT and/or mercapto mix.

Regarding some other rubber allergens, thioureas were infrequent allergens, with only 0.4% positive reactions in the whole study group, and not significantly more in the healthcare worker subgroup.

1,3-Diphenylguanidine (1,3-DPG) elicited positive reactions in 3.0% of the patients. Of the 77 positive reactions, 65 were +, and 12 were strongly positive (+++) or +++. In addition, 93 doubtful or irritant reactions were observed. Hence, the RI was −0.1, and the PR was 84%. For comparison, the RIs and PRs of thiurams, ZDEC, MBT and MBT derivatives ranged from +0.2 to +0.7 and from 53% to 69%, respectively (data not shown in detail). In Figs. 1 and 2, frequencies of reactions to four chemical groups, that is, thiurams, dithiocarbamates, MBT and its derivatives, and thioureas, as well as to 1,3-DPG, over the years in the whole study group and in the healthcare worker subgroup are shown. Some variation across the years of the study period can be seen, but no consistent time trend. Most impressive is a temporary drop of thiuram sensitization prevalence in 2006. However, reaction frequencies in 2010 were very similar to those observed in 2002; hence, no overall trend can be seen.

Thiurams and dithiocarbamates, which are chemically closely related, were patch tested in parallel in 3301 patients; of these, 1018 were healthcare workers. Among all patients, 430 (13.0%) reacted to thiurams, and 112 (3.4%) reacted to dithiocarbamates. One hundred and four patients reacted to both groups of accelerators, that is, 93% (95% CI 86–97%) of those reacting to dithiocarbamates, but only 24% (95% CI 20–29%) of those reacting to thiurams (p < 0.0001; McNemar’s test for asymmetry). When the analysis was focused on concomitant reactions to two particularly closely related compounds, namely ZDEC and tetraethylthiuram disulfide (TETD), the results were as follows. Both compounds were patch tested in 2280 patients. Of these, 208 reacted to TETD, and 85 to ZDEC. In 76 patients, positive reactions to both compounds were observed: 89% (95% CI 81–95%) of those reacting to ZDEC,
Table 2. Patch test reactions to rubber allergens in patients with occupational contact dermatitis and suspected glove allergy

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Occupational dermatitis patients (n = 3448)</th>
<th>Subgroup of healthcare workers with occupational dermatitis (n = 1058)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients tested</td>
<td>Patients with positive reactions</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Thiurams (at least one of 1–5)</td>
<td>3306</td>
<td>431</td>
</tr>
<tr>
<td>1. Thiuram mix</td>
<td>3070</td>
<td>341</td>
</tr>
<tr>
<td>2. Tetraethylthiuram disulfide (CAS 97-77-8)</td>
<td>2474</td>
<td>229</td>
</tr>
<tr>
<td>3. Tetramethylthiuram monosulfide (CAS 97-74-5)</td>
<td>2478</td>
<td>185</td>
</tr>
<tr>
<td>4. Tetramethylthiuram disulfide (CAS 137-26-8)</td>
<td>2479</td>
<td>128</td>
</tr>
<tr>
<td>5. Dipentamethylenethiuram disulfide (CAS 94-37-1)</td>
<td>2479</td>
<td>90</td>
</tr>
<tr>
<td>Dithiocarbamates (at least one of 6–8)</td>
<td>3319</td>
<td>115</td>
</tr>
<tr>
<td>6. Zinc diethyldithiocarbamate (CAS 14324-55-1)</td>
<td>3119</td>
<td>111</td>
</tr>
<tr>
<td>7. Zinc dibutyldithiocarbamate (CAS 136-23-2)</td>
<td>2495</td>
<td>5</td>
</tr>
<tr>
<td>8. Zinc dibenzyldithiocarbamate (CAS 14726-36-4)</td>
<td>2303</td>
<td>4</td>
</tr>
<tr>
<td>Mercaptobenzothiazole and its derivatives (at least one of 9–13)</td>
<td>3323</td>
<td>100</td>
</tr>
<tr>
<td>9. Mercapto mix 1% pet.</td>
<td>3070</td>
<td>64</td>
</tr>
<tr>
<td>10. Mercaptobenzothiazole (CAS 149-30-4)</td>
<td>3112</td>
<td>72</td>
</tr>
<tr>
<td>11. Morpholinyl mercaptobenzothiazole (CAS 102-77-2)</td>
<td>2556</td>
<td>56</td>
</tr>
<tr>
<td>12. N-cyclohexyl-2-benzothiazylsulfenamide (CAS 95-33-0)</td>
<td>2480</td>
<td>39</td>
</tr>
<tr>
<td>13. Dibenzothiazyl disulfide (CAS 120-78-5)</td>
<td>2481</td>
<td>24</td>
</tr>
<tr>
<td>Thioureas (at least one of 14–15)</td>
<td>2487</td>
<td>11</td>
</tr>
<tr>
<td>14. Diphenylthiourea (CAS 102-08-9)</td>
<td>2479</td>
<td>7</td>
</tr>
<tr>
<td>15. Dibutylthiourea (CAS 109-46-6)</td>
<td>2473</td>
<td>5</td>
</tr>
<tr>
<td>16. 1,3-Diphenylguanidine (CAS 102-06-7)</td>
<td>2578</td>
<td>77</td>
</tr>
</tbody>
</table>


and 37% (95% CI 30–43%) of those reacting to TETD, respectively.

Of the thiuram-positive patients, 207 had a strong positive reaction (+++ or ++++) to at least one thiuram or the thiuram mix. Of these 207 patients, 71 (34%; 95% CI 28–41%) reacted to dithiocarbamates. In contrast, only 33 of those 223 patients (15%; 95% CI 10–20%) with a weak positive reaction (i.e. +) to thiurams also reacted to dithiocarbamates. The difference was statistically significant ($p < 0.0001$; Fisher’s exact test). Conversely, of the 112 patients reacting to dithiocarbamates, 78 had a weak (i.e. +) and 34 a strong (+++, ++++) reaction to at least one dithiocarbamate. Seventy-four of the 78 patients (95% (95% CI 87–99%)) and 30 of the 34 patients (88% (95% CI 73–98%)) also reacted to thiurams. The difference was not significant ($p = 0.24$; Fisher’s exact test).

Among healthcare workers, the proportions were as follows: 152 patients reacted to thiurams (14.9%), and 34 (3.3%) reacted to dithiocarbamates. All 34 patients of the latter group, who represent 22.4% of the thiuram-positive patients, also reacted to thiurams.

Combinations of reactions to three different chemical groups of accelerators are shown in Table 3. Altogether, 3295 occupational dermatitis patients and, as a subgroup of these, 1015 healthcare workers were patch tested with thiurams, dithiocarbamates, and MBT and its derivatives. It can be seen that sensitization to MBT and its derivatives was combined with thiuram sensitization in only approximately one-third of the patients (33 of 98, and 8 of 22, respectively). Combined sensitization to dithiocarbamates and MBT and its derivatives occurred in 9 patients, who were not healthcare workers. All of these patients were also sensitized to thiurams.

![Fig. 1. Sensitization to rubber allergens in patients with occupational contact dermatitis and suspected glove allergy. 1,3-DPG, 1,3-diphenylguanidine; MBT, mercaptobenzothiazole.](image-url)
Fig. 2. Sensitization to rubber allergens in healthcare workers with occupational contact dermatitis and suspected glove allergy. 1,3-DPG, 1,3-diphenylguanidine; MBT, mercaptobenzothiazole.

Discussion

The most important result of our analysis is that there is no significant change in contact allergy to accelerators in patients with occupational dermatitis and suspected glove allergy. As before, thiurams are the most frequent sensitizers in this context, whereas sensitization to dithiocarbamates and/or MBT and its derivatives is far less frequent, and thioureas are, altogether, rare sensitizers.

Thiurams

We have no explanation for the temporary decline in thiuram reactions in 2006. In additional exploratory data analyses (not shown here), no reason for this transient effect could be found. Thiurams are well-established and relatively cheap ingredients used for vulcanization of rubber gloves. Hence, cheap latex or nitrile gloves, which are, according to our knowledge and experience, particularly used in healthcare, probably still contain thiurams – in contrast to most brands of more expensive gloves offered by several renowned producers on the European market. The latter can be seen in the medical glove lists published by the test laboratory for latex products at the department of dermatology of the University of Erlangen (http://www.hautklinik.uk-erlangen.de/e1846/e1901/index Ger.html). In these lists, not only the protein contents but also the accelerators of the respective gloves are noted. Because our data analysis was focused on the particular subgroup of occupational dermatitis patients with suspected glove allergy, we cannot confirm the published observations of a downward trend in thiuram sensitization among healthcare workers (5, 8). However, the results are difficult to compare, as the present study sample is a highly selected subgroup of all patients patch tested. For instance, whereas the prevalence of contact sensitization to thiuram mix in non-selected healthcare workers ranged from 3% to ∼5% in the previous analysis (5), albeit only covering 2002–2006, the prevalence of sensitization to this screening allergen is now 13% in healthcare workers (Table 2). Our results indicate that this problem still is unsolved.

To prevent further thiuram sensitization, the use of thiuram-free gloves should be promoted. The introduction of an accelerator-free medical glove is a milestone in this context, and will hopefully lead to a significant reduction in rubber glove allergy.

As published before (15), our results confirm that not every case of thiuram sensitization is detected by the thiuram mix. Approximately 20% of the thiuram-sensitized patients are missed by the mix. Therefore, it is advisable to patch test not only with the baseline series but also with the rubber series in cases of suspected rubber glove allergy.

Dithiocarbamates

The frequency of sensitization to a chemical depends on its usage and its sensitizing potency. As mentioned

Table 3. Single and combined sensitization to different groups of accelerators in all patients with occupational dermatitis related to glove use, and in the subgroup of healthcare workers

<table>
<thead>
<tr>
<th>Reaction to:</th>
<th>Thiurams</th>
<th>Dithiocarbamates</th>
<th>MBT and its derivatives</th>
<th>Occupational dermatitis patients (n = 3295)</th>
<th>Subgroup of healthcare workers with occupational dermatitis (n = 1015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>299</td>
<td>108</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>65</td>
<td>14</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>95</td>
<td>34</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

MBT, mercaptobenzothiazole; +, positive reactions; −, negative, doubtful and irritant reactions.
above, exposure to thiurams was very probably still much more extensive than exposure to dithiocarbamates in our study population, explaining the much higher frequency of thiuram sensitization. The sensitizing potencies of dithiocarbamates and thiurams are probably similar. In the local lymph node assay (LLNA) in mice, ZDEC proved to be more potent than TETD (16). However, the skin sensitization potency of zinc dibutyl dithiocarbamate seemed to be very low in the same experimental setting (17).

Dithiocarbamates are chemically closely related to thiurams; simplified, a dithiocarbamate is one-half of the corresponding thiuram molecule (7). Our data show that sensitization to dithiocarbamates is almost always combined with thiuram sensitization. In contrast, only about one-quarter of the thiuram-positive patients also react to dithiocarbamates. When focusing on the chemically very closely related combination TETD/ZDEC, we also found that almost all patients who reacted to the dithiocarbamate (ZDEC) also reacted to the corresponding thiuram (TETD). However, the proportion of ZDEC-positive patients among those reacting to TETD was higher than the proportion of dithiocarbamate-positive patients among those reacting to at least one thiuram or the thiuram mix (37% versus 24%). Among patients with a strong positive reaction (++ or ++++) to thiurams, concomitant reactions to dithiocarbamates were noted twice as often as among those with a weak positive reaction (+) to thiurams. Three possible explanations for these observations may be considered, keeping in mind the limitations of clinical studies, with unknown exposure and induction conditions of patients (as opposed to controlled animal experiments). (i) In a certain proportion of thiuram-allergic patients, especially those with high-grade sensitization, true immunological cross-reactions to dithiocarbamates may occur, based on the close chemical relationship of the compounds. (ii) By oxidation processes, thiurams may be formed, to some extent, from dithiocarbamates on and in the skin, leading to allergic reactions in patients with high-grade sensitization to thiurams. (iii) Co-sensitization to thiurams and dithiocarbamates may be acquired by synchronous or metachronous co-exposure to both groups of chemicals through the wearing of different brands of rubber gloves.

**MBT and its derivatives**

It is known that MBT derivatives are metabolized or otherwise converted to MBT in the skin, and that MBT is the responsible allergen in contact allergy to MBT derivatives (18, 19). MBT is known to exist partly in the form of its thioester tautomer, which can react as an electrophile with nucleophilic groups in proteins (20, 21), especially free thiol groups, as in cysteine residues (22, 23). In an oxidizing environment such as a buffer solution, MBT can also be converted to the dimeric dibenzothiazyl disulfide (18). Dibenzothiazyl disulfide may likewise interact with sulphydryl moieties in peptides, forming relatively stable mixed disulfides (19, 24) that may be recognized by the immune competent cells. However, in accordance with previous results (25), we could demonstrate that, by patch testing with MBT only, approximately one quarter of the patients concerned would be missed. With mercapto mix only, this proportion would be about one-third (Table 2). Concomitant reactivity between MBT and mercapto mix is far from perfect. With the combination of both, better sensitivity was achieved: 86% of the patients concerned were detected. Therefore, it is justified to keep both MBT and mercapto mix in the baseline series (25). Additionally, it is advisable to patch test with the rubber series in cases of suspected MBT allergy, because 14% of the patients eventually diagnosed with contact allergy to MBT or its derivatives would be missed if only the two screening agents were used.

**Thioureas**

Thioureas are used in the production of synthetic rubbers, particularly neoprene products (26). According to our information, thioureas are only rarely used as accelerators in protective rubber gloves. This is reflected by the low frequency of sensitization in our study group. Additionally, dibutylthiourea and diphenylthiourea had very low skin sensitization activity in the standard LLNA in mice (27, 28), and clear-cut positive results were only obtained in a more sensitive LLNA with intradermal application (27), but, recently, the possible metabolic activation of diphenylthiourea has been discussed and studied (28).

**1,3-Diphenylguanidine**

Patch testing with 1,3-DPG is hampered by the low diagnostic quality of the common test preparation 1,3-DPG 1% pet. (14). As described previously, its RI is below zero (−0.1) and its PR is very high (84%), characterizing this test preparation as a ‘problematic allergen’. Positive reactions, in particular weak positive reactions, to 1,3-DPG 1% pet. have to be interpreted very carefully. 1,3-DPG is used in rubber glove production, and there are cases of true allergic sensitization (29), but the majority of cases are probably false-positive reactions. Parallel
Multiple reactions

Considering secondary prevention, allergic reactions to accelerators of different chemical groups were the exception, and not the rule (except for the combination of thiurams and dithiocarbamates), enabling the patient to switch to protective gloves that do not contain the allergen(s) to which they are allergic. Approximately three-quarters of the thiuram-sensitized patients did not react to dithiocarbamates; hence, for them, dithiocarbamate-containing, but thiuram-free, gloves may be an alternative. Of course, switching to a glove brand without both thiurams and dithiocarbamates should be preferred (31). However, the range of such gloves is much smaller than that of dithiocarbamate-containing gloves without thiurams. MBT allergy is rarely combined with thiuram allergy, so there should be an alternative in case of sensitization to either of these. Accelerator-free gloves are the best alternative for patients with multiple rubber contact allergy.

Conclusion

Contact allergy to accelerators in elastic protective gloves is still frequent, and the spectrum of responsible allergens has remained largely unchanged during the last 17 years. As it is presently difficult for the consumer to obtain information about accelerators contained in the various gloves, we suggest the introduction of mandatory labelling of these chemicals, at least by group names (e.g. ‘contains thiurams’), on the glove package. Ideally, this labelling should be supplemented with policing by regulators, as information on the accelerators given by the producers does not always reflect the results of chemical analyses of rubber glove samples (32).

References

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