Methyldibromoglutaronitrile is an important contact allergen in The Netherlands

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From 15 May to 15 December 1994, 2943 patients suspected of having contact dermatitis (1955 women, 988 men) were patch tested with methyldibromoglutaronitrile 0.3%, 0.1% and 0.05% pet. 119 patients (4.0%; women 4.1%, men 3.8%) proved to be allergic. 71% of the reactions were considered to be relevant. In 2/3 of the patients, causative products were cosmetics, in 1/3 moistened toilet tissues. Testing with methyldibromoglutaronitrile at lower concentrations (0.05% and 0.1%) and with commercial allergens (Euxyl® K 400 and methyldibromoglutaronitrile, both containing methyldibromoglutaronitrile 0.1%), resulted in a number of false-negative reactions. All preservatives in the European standard series had lower scores than the 4% positive reactions to methyldibromoglutaronitrile (formaldehyde 2.0%, MCI/MI (Kathon® CG) 3.2%, parabens 1.0%, quat-erum-15 1.3%). It is concluded that methyldibromoglutaronitrile (present in the commercial preservative Euxyl® K 400) is an important contact allergen in the Netherlands in cosmetics and moistened toilet tissues. It should be added to cosmetics series and to proctological series. The optimal test concentration is unknow, but may be 0.3% pet. The concentration of 0.1% methyldibromoglutaronitrile in the currently available commercial allergens appears to be too low, resulting in a number of false-negative reactions.

Key words: methyldibromoglutaronitrile; Euxyl® K 400; preservatives; 1,2-dibromo-2,4-dicyanobutane; contact allergy; cosmetics; moistened toilet tissues; patch testing technique. © Munksgaard, 1996.

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In 1991, the Dutch Contact Dermatitis group found a 0.5% frequency of positive reactions to methyldibromoglutaronitrile (1,2-dibromo-2,4-dicyanobutane) in patients suspected of having contact dermatitis (1). At that time, it was decided to repeat the study after some years, to monitor its possible emergence as an important contact allergen, as methyldibromoglutaronitrile was rapidly gaining popularity in the cosmetics industry as a substitute for methyl (chloro) isothiazolinone (Kathon® CG). The latter preservative was, in many European countries, one of the most common allergens (2).

The repeat study, performed in 1994, aimed at determining the current frequency of contact allergy to methyldibromoglutaronitrile, identifying the products that cause dermatitis and exploring the influence of test concentrations on the patch test results.

Materials and Methods
From 15 May to 15 December 1994, methyldibromoglutaronitrile was added to the European standard series and tested in all patients suspected of having contact dermatitis by the participating members of the Dutch Contact Dermatitis Workgroup. The allergens were prepared by the Regional Inspectorate for Health Protection, Department of Cosmetics, Enschede (JWW). Concentrations were 0.05%, 0.1% and 0.3% w/w; soy lecithin was added to obtain homogeneous dispersions. Therefore, soy lecithin 5% was also tested in all patients. In some hospitals, Euxyl® K 400 0.5% pet. (Chemotechnique, containing 0.1% methyldibromoglutaronitrile) and/or methyldibromoglutaronitrile 0.1% pet. (Trolab) were also tested.

The following data were recorded for all patients tested: sex, age and reactions to preservatives in
Table 1. Results and evaluation of patch testing with methyldibromoglutaronitrile

<table>
<thead>
<tr>
<th>Description</th>
<th>No. of patients tested:</th>
<th>Range(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients tested</td>
<td>2943</td>
<td>(range 159-447)</td>
</tr>
<tr>
<td>Number of women</td>
<td>1955 (66%)</td>
<td>(range 62%-72%)</td>
</tr>
<tr>
<td>Number of men</td>
<td>988 (34%)</td>
<td>(range 28%-38%)</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>8-86</td>
<td>(range 29-43 year)</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Total number of positive reactions:</td>
<td>119</td>
<td></td>
</tr>
<tr>
<td>Total number of positive reactions in women:</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Total number of positive reactions in men:</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>% of patients positive</td>
<td>4.0%</td>
<td>(range 1.4%-12%)</td>
</tr>
<tr>
<td>% of women positive</td>
<td>4.1%</td>
<td>(range 1.8%-12.5%)</td>
</tr>
<tr>
<td>% of men positive</td>
<td>3.8%</td>
<td>(range 0%-11.1%)</td>
</tr>
<tr>
<td>Number of relevant reactions:</td>
<td>84 (71%)</td>
<td>(range 40%-100%)</td>
</tr>
<tr>
<td>Relevant products: cosmetics:</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Reactions to different concentrations of methyldibromoglutaronitrile:</td>
<td>0.3% :115</td>
<td></td>
</tr>
<tr>
<td>Reactions to different concentrations of methyldibromoglutaronitrile:</td>
<td>0.1% :103</td>
<td></td>
</tr>
<tr>
<td>Reactions to different concentrations of methyldibromoglutaronitrile:</td>
<td>0.05%:85</td>
<td></td>
</tr>
<tr>
<td>% of positive reactions with commercial Euxyl(^b) K 400 0.5%:</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>% of positive reactions with commercial methyldibromoglutaronitrile 0.1% pet.:</td>
<td>73%</td>
<td></td>
</tr>
</tbody>
</table>

Reactions to methyldibromoglutaronitrile compared with other preservatives in the European standard series:

<table>
<thead>
<tr>
<th>Preservative</th>
<th>% of positive reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>methyldibromoglutaronitrile</td>
<td>4.0%</td>
</tr>
<tr>
<td>formaldehyde</td>
<td>2.0%</td>
</tr>
<tr>
<td>Kathon(^\text{®}) CG (MI/MCI)</td>
<td>3.2%</td>
</tr>
<tr>
<td>parabens</td>
<td>1.0%</td>
</tr>
<tr>
<td>quaternium-15</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

\(^a\) Range refers to the results in the various participating hospitals.

\(^b\) One centre had a far higher % of positive reactions (12%) than all others: this is a tertiary referral centre with many occupational dermatitis patients, especially hairdressers.

Discussion

Euxyl\(^\text{®}\) K 400 (Schulke & Mayr, Hamburg, Germany) is a relatively new preservative, used in cosmetics for some 10 years. It contains 2 active ingredients: 80% phenoxyethanol and 20% methyldibromoglutaronitrile (1,2-dibromo-2,4-dicyanobutane). After the 1st report of contact dermatitis in 1989 (3), several studies have documented cases of contact allergy, especially in Italy (4-6), Germany (7, 8) and The Netherlands (1, 9). Hausen (10) provided a review of the literature up to 1992. The allerg-
Addition of a rarely sensitizing emulsifier, such as sorbitan sesquioleate, does not induce irritant reactions or sensitization. Therefore, the optimal test concentration may be 0.3–0.5%. Addition of a rarely sensitizing emulsifier, such as soy lecithin, is advisable for facilitating homogeneous dispersion. Possibly, as sorbitan sesquioleate does for the fragrance mix (12), such an addition may enhance the sensitivity of the test system.

References


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