

## PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/22488>

Please be advised that this information was generated on 2017-12-05 and may be subject to change.

# Methyldibromoglutaronitrile is an important contact allergen in The Netherlands

ANTON C. DE GROOT<sup>1</sup>, PAUL A. J. J. M. DE COCK<sup>2</sup>, PIETER JAN COENRAADS<sup>3</sup>,  
CORNELIS J. W. VAN GINKEL<sup>4</sup>, BEREND A. JAGTMAN<sup>5</sup>, THEODOOR VAN JOOST<sup>6</sup>,  
A. M. JOOST VAN DER KLEY<sup>7</sup>, MARCUS M. H. M. MEINARDI<sup>8</sup>, GERARD SMEENK<sup>9</sup>,  
PIETER G. M. VAN DER VALK<sup>10</sup>, HENK B. VAN DER WALLE<sup>11</sup> AND JAN WILLEM WEYLAND<sup>12</sup>

<sup>1</sup>Carolus-Liduna Ziekenhuis, P.O. Box 1101, 5200 BD's-Hertogenbosch, The Netherlands  
Dutch Contact Dermatitis Group: <sup>2</sup>Den Haag, <sup>3</sup>Groningen, <sup>4</sup>Utrecht, <sup>5</sup>Venlo, <sup>6</sup>Rotterdam,  
<sup>7</sup>Maastricht, <sup>8</sup>Amsterdam, <sup>9</sup>Deventer, <sup>10</sup>Nijmegen, <sup>11</sup>Arnhem, <sup>12</sup>Enschede

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<sup>®</sup> 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<sup>®</sup> CG) 3.2%, parabens 1.0%, quaternium-15 1.3%). It is concluded that methyldibromoglutaronitrile (present in the commercial preservative Euxyl<sup>®</sup> 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 unknown, 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<sup>®</sup> K 400; preservatives; 1,2-dibromo-2,4-dicyanobutane; contact allergy; cosmetics; moistened toilet tissues; patch testing technique. © Munksgaard, 1996.

*Accepted for publication 16 June 1995*

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<sup>®</sup> 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 pet.; soy lecithin was added to obtain homogeneous dispersions. Therefore, soy lecithin 5% was also tested in all patients. In some hospitals, Euxyl<sup>®</sup> 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

		Range <sup>a)</sup>
No. of patients tested:	2943	(range 159-447)
number of women	1955 (66%)	(range 62%-72%)
number of men	988 (34%)	(range 28%-38%)
Age range (years)	8-86	
Average age (years)	38	(range 29-43 year)
Total number of positive reactions:	119	
Total number of positive reactions in women:	81	
Total number of positive reactions in men:	38	
% of patients positive:	4.0%	(range 1.4%-12%) <sup>b)</sup>
% of women positive:	4.1%	(range 1.8%-12.5%)
% of men positive:	3.8%	(range 0%-11.1%)
Number of relevant reactions:	84 (71%)	(range 40%-100%)
Relevant products: cosmetics:	60	
moistened toilet tissues:	30	
Reactions to different concentrations of methyldibromoglutaronitrile:	0.3% :115	
	0.1% :103	
	0.05%:85	
% of positive reactions with commercial Euxyl <sup>®</sup> K 400 0.5%:	69%	
% of positive reactions with commercial methyldibromoglutaronitrile 0.1% pet.:	73%	
Reactions to methyldibromoglutaronitrile compared with other preservatives in the European standard series:		
methyldibromoglutaronitrile	4.0%	(range 1.4%-12%)
formaldehyde	2.0%	(range 0.0%-3.8%)
Kathon <sup>®</sup> CG (MI/MCI)	3.2%	(range 0.6%-7.2%)
parabens	1.0%	(range 0.0%-3.8%)
quaternium-15	1.3%	(range 0.4%-2.2%)

<sup>a)</sup> Range refers to the results in the various participating hospitals.

<sup>b)</sup> 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.

the European standard series (formaldehyde, MCI/MI (Kathon<sup>®</sup> CG), parabens, quaternium-15). For patients reacting to 1 or more preparations of methyldibromoglutaronitrile, the following data were recorded: sex, age, localization of dermatitis, patch test data, relevance of the positive reaction and causative product(s).

### Results

The results of patch testing are summarized in Table 1. A total of 2943 patients were patch tested: 1955 (66%) women and 988 (34%) men. Their ages ranged from 8-86 years, with an average of 38 years.

119 patients (4.0%) had positive reactions to 1 or more concentrations of methyldibromoglutaronitrile; the % of positive reactions in women was 4.1%, in men 3.8%. Of the 119 positive reactions, 84 (71%) were considered to be relevant. In 60 patients, cosmetics were the cause of the dermatitis; in 30 cases, moistened toilet tissue was traced as the source of the allergen (in 6, both cosmetics and toilet paper were implicated).

Of the 119 patients allergic to methyldibromoglutaronitrile, 115 reacted to 0.3%, 103 to 0.1%

and 85 to 0.05%. Of the allergic patients who were also tested with the commercial preparation Euxyl<sup>®</sup> K 400 0.5% pet. (Chemotechnique), 69% reacted to it. For the commercial allergen methyldibromoglutaronitrile (Trolab) 0.1% pet., the % of positive reactions was 73. No irritant reactions were observed to any concentration of methyldibromoglutaronitrile.

The scores of positive reactions to other preservatives in the European standard series were 3.2% for MCI/MI (Kathon CG), 2.0% for formaldehyde, 1.3% for quaternium-15 and 1.0% for parabens.

### Discussion

Euxyl<sup>®</sup> 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 aller-



gen in Euxyl® K 400 is virtually always methyldibromoglutaronitrile. The causative products are cosmetics and, notably in the Netherlands, moistened toilet tissues (1, 9).

In this 1994 study, we found a prevalence of contact allergy to methyldibromoglutaronitrile of 4% in a multicentre investigation of 2943 patients suspected of having contact dermatitis. Women (4.1%) and men (3.8%) were equally affected, the allergenic products being mainly cosmetics in women and moistened toilet tissues in men.

In 4 years, the prevalence of allergy to methyldibromoglutaronitrile in the Netherlands has increased from 0.5% to 4.0%. There are 2 important determining factors. 4 years ago, we tested methyldibromoglutaronitrile at 0.05% pet. Our present results clearly show that this % is too low: only 85 of 119 allergic patients (71%) reacted to it. Thus, the actual prevalence in 1991 may have been underestimated. Secondly, the market penetration of Euxyl® K 400 has rapidly increased. In 1990, 13% of cosmetic products sold in the Netherlands contained the preservative (1). Currently, an estimated 25–35% of cosmetic products are preserved with Euxyl® K 400, among which are some of the best selling brands in the main product categories. In addition, in 1994, methyldibromoglutaronitrile was found to be present in 15 of 24 (63%) brands and types of moist toilet paper (11).

From this study, we conclude that methyldibromoglutaronitrile is an important contact allergen in the Netherlands, from its presence in cosmetics and moistened toilet tissues. Its current rate of sensitization exceeds that of all preservatives in the European standard series, including (in 9 of the 11 hospitals ) methyl (chloro) isothiazolinone (Kathon® CG). Therefore, it should be added to cosmetics series and to protological series. In countries where, as in the Netherlands, contact allergy to methyldibromoglutaronitrile is frequent, the allergen should be added to the European standard series.

The 2nd conclusion concerns the test concentration. Our results suggest that using test concentrations of 0.1% and lower, which also holds true for the currently-available commercial test allergens methyldibromoglutaronitrile 0.1% and Euxyl® K 400 0.5% (containing 0.1% methyldibromoglutaronitrile), is likely to result in false-negatives. The data provided by Tosti et al. (6) suggest that

0.5% methyldibromoglutaronitrile, 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

1. De Groot A C, Bruynzeel D P, Coenraads P J et al. Frequency of allergic reactions to methyldibromoglutaronitrile (1,2-dibromo-2,4-dicyanobutane) in The Netherlands. *Contact Dermatitis* 1991; 25: 270–271.
2. De Groot A C, Herxheimer A. Isothiazolinone preservative: cause of a continuing epidemic of cosmetic dermatitis. *The Lancet* 1989; i: 314–316.
3. Senff H, Exner M, Gortz J, Goos M. Allergic contact dermatitis from Euxyl K 400. *Contact Dermatitis* 1989; 20: 381.
4. Tosti A, Guerra L, Bardazzi F, Gasparri F, Euxyl K 400: a new sensitizer in cosmetics. *Contact Dermatitis* 1991; 25: 89–93.
5. Motolese A, Seidenari S, Truzzi M, Giannetti A. Frequency of contact sensitization to Euxyl K 400. *Contact Dermatitis* 1991; 25: 128.
6. Tosti A, Vincenzi C, Trevisi P, Guerra L. Euxyl K 400: incidence of sensitization, patch test concentration and vehicle. *Contact Dermatitis* 1995; 33: 193–195.
7. Fuchs T et al. Contact allergy to Euxyl K 400. *Dermatosen* 1991; 39: 151–153.
8. Schubert H, Prater E. Kontaktallergie auf Konservierungsmittel im Gebiet der ehemaligen DDR. *Z Hautkr* 1992; 67: 330–333.
9. Van Ginkel C J W, Rundervoort G J. Increasing contact allergy from the new preservative 1,2-dibromo-2,4-dicyanobutane (methyldibromoglutaronitrile). *Br J Dermatol* 1995; in press.
10. Hausen B M. The sensitizing potency of Euxyl® K 400 and its components 1,2-dibromo-2,4-dicyanobutane and 2-phenoxyethanol. *Contact Dermatitis* 1993; 28: 149–153.
11. Rooselaar J, Stern A G, Weijland J W. *Onderzoek naar de aanwezigheid van methylisothiazolinon, chloormethylisothiazolinon en methyldibromoglutaronitrile in vochtig toiletpapier*. Enschede: Inspectie Gezondheidsbescherming Keuringsdienst van Waren, 1994.
12. Frosch P J, Pilz B, Burrows D et al. Testing with fragrance mix. Is the addition of sorbitan sesquioleate to the constituents useful? *Contact Dermatitis* 1995; 32: 272–277.

Address:

A. C. de Groot  
 Carolus-Liduína Ziekenhuis  
 P.O. Box 1101  
 5200 BD's-Hertogenbosch  
 The Netherlands