

Decreasing trends in methyldibromo glutaronitrile contact allergy – following regulatory intervention

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Background: The preservative methyldibromo glutaronitrile (MDBGN) has been banned, first from stay-on, and later from rinse-off cosmetics, in the EU countries because of increasing rates of contact allergy.

Objectives: To evaluate the frequency of contact allergy to MDBGN among patients patch tested by the Danish Contact Dermatitis Group just before and following regulatory decisions.

Patients/Methods: The data set comprised 19 279 consecutive eczema patients patch tested from 2003–2007 with MDBGN 0.3% in petrolatum (pet.) or, in a minority of patients, with Euxyl KTM 400 1.5% in pet.

Results: A significantly decreasing trend in the frequency of positive patch tests to MDBGN was found from 4.6% in 2003 to 2.6% in 2007 ($P < 0.001$). The decreasing trend was seen for both men and women. A significantly decreasing proportion of cases with a current relevance of contact allergy to MDBGN was also seen from 51.3% in 2003 to 29% in 2007 ($P < 0.001$).

Conclusions: Regulatory interventions have already had a major effect on allergic disease due to MDBGN in Denmark. The same trends are likely to be seen in other EU countries.

Key words: epidemiology; patch test; preservatives; prevention; sensitization. © Blackwell Munksgaard, 2008.

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The preservative methyldibromo glutaronitrile (MDBGN) was launched in the 1980s for use in industrial and cosmetic products. It was approved for use in cosmetics in a concentration of 0.1%. Soon after introduction to the market, the first case of contact allergy was reported in a worker exposed to glue preserved with MDBGN (1) and cases in consumers using cosmetic products followed (reviewed in 2).

De Groot et al. showed that the frequency of contact allergy to MDBGN in the Netherlands increased from 0.5% in 1991 to 4% in 1994 (3).

Similarly, an increased rate of patch test reactivity to MDBGN was reported from London (4), and in a study that involved 16 centres in Europe, the rate of positive reactions increased from 0.7% in 1991 to 3.5% in 2000 (5). Exposures were primarily consumer products such as stay-on and rinse-off cosmetics (6–9) and moist toilet paper/wipes (10, 11). In light of these findings, and based on the advice from the Scientific Committee on Non-Food Products, a change to the Cosmetic Directive was made in 2005, limiting the use of MDBGN to rinse-off products (12). Following

accumulated evidence of the role of rinse-off products in contact allergy to MDBGN, this decision was revised in 2007 to include a legal prohibition on the use of MDBGN in rinse-off products also (13).

Clinical epidemiological data from patch-tested patients play a key role in identifying problematic use of contact allergens because of insufficient risk assessment prior to product marketing, but also in assessing the effect of interventions such as regulations (14). The Danish Contact Dermatitis Group (DCDG) has previously reported data on the incidence of contact allergy to MDBGN (6). The aim of the present study was to evaluate the frequency of contact allergy to MDBGN among patients patch tested by the DCDG just before and following regulatory decisions.

Materials and Methods

In 2003, the DCDG established a surveillance network comprising both hospital departments and dermatologists in private practice. The hospital departments and the clinics are distributed all over Denmark. The data set for the current investigation comprised 19 279 consecutive eczema patients patch tested from 2003 to 2007. A total of 12 639 (65%) were women and 6640 (35%) were men; 10% had occupational disease, 15% a personal history of atopic dermatitis, 36% hand eczema, 6% eczema of the lower leg, 18% facial eczema, and 58% were over 40 years of age (Table 1). The distribution was comparable to other investigations (15).

It is estimated that 25 000 patients are patch tested in Denmark every year (16). Thus, the current sample comprised about 15% of the total patch-tested population.

All patients included were patch tested with an extended version of the European baseline series of contact allergens, including MDBGN 0.3% in pet. (Hermal, Reinbek, Germany), except for a minority of patients who were tested with Euxyl K 400 (Schülke & Mayr, Hamburg, Germany) 1.5% in pet. (comprising 0.3% MDBGN and 1.2% phenoxyethanol). MDBGN was applied

using Finn Chambers[®] (Epitest, Tuusula, Finland) on Scanpor[®] (Norgesplaster A/S, Vennesla, Norway). The patches were left for 2 days. Readings were performed at a minimum on D3 using the International Contact Dermatitis Research Group scale (17) with a positive patch test reaction defined as a minimum homogeneous infiltration and erythema covering the test area, corresponding to a one-plus reaction.

Since 2005, MDBGN at 0.5% w/w in pet. has been recommended for the European baseline series (18). However, in the current investigation, 0.3% MDBGN was used in the entire study period to follow trends in the rate of positive reactions.

Current relevance was assessed in each case and was based on the patient's history and in some cases combined with use tests, chemical analysis, and/or presence of MDBGN on the list of ingredients of one or more cosmetic products used by the patient.

Statistics

The chi-squared test for trend was used to assess the trend in frequency. A *P* value of <0.05 was considered statistically significant.

Results

A significantly decreasing trend in the frequency of positive patch test reactions to MDBGN from 4.6% in 2003 to 2.6% in 2007 was found (*P* < 0.001). The decrease from 4.9% to 3.1% in men was also statistically significant (*P* < 0.05), as was the decrease in women from 4.4% in 2003 to 2.4% in 2007 (*P* < 0.001) (Fig. 1).

The number of centres participating in the study increased from seven in 2003 to 10 in 2005–2007; however, an analysis of the data from the seven original centres showed similar significantly decreasing trends, as for all 10 centres.

Current relevance was found in 39.7% of the cases with a significantly decreasing trend from 51.3% in 2003 to 29.0% in 2007 (*P* < 0.001). The proportion of cases where MDBGN was

Table 1. Background variables for the tested population (19 279 consecutive eczema patients)

	2003, <i>n</i> (%)	2004, <i>n</i> (%)	2005, <i>n</i> (%)	2006, <i>n</i> (%)	2007, <i>n</i> (%)
Men	1217 (35.1)	1239 (33.6)	1464 (34.9)	1445 (35.3)	1275 (33.0)
Occupational	238 (6.9)	366 (9.9)	501 (12.0)	436 (10.6)	494 (12.0)
Atopic dermatitis	442 (12.7)	493 (13.4)	712 (17.0)	700 (17.1)	653 (16.0)
Hand eczema	1263 (36.4)	1272 (34.5)	1537 (36.7)	1504 (36.7)	1407 (36.0)
Leg eczema	280 (8.1)	245 (6.6)	262 (6.3)	237 (5.8)	158 (4.0)
Facial eczema	623 (18.0)	650 (17.6)	845 (20.2)	749 (18.3)	692 (17.0)
Age above 40 years	1983 (57.2)	2173 (58.9)	2478 (59.2)	2412 (58.9)	2236 (58.0)
Total	3463	3688	4188	4091	3849

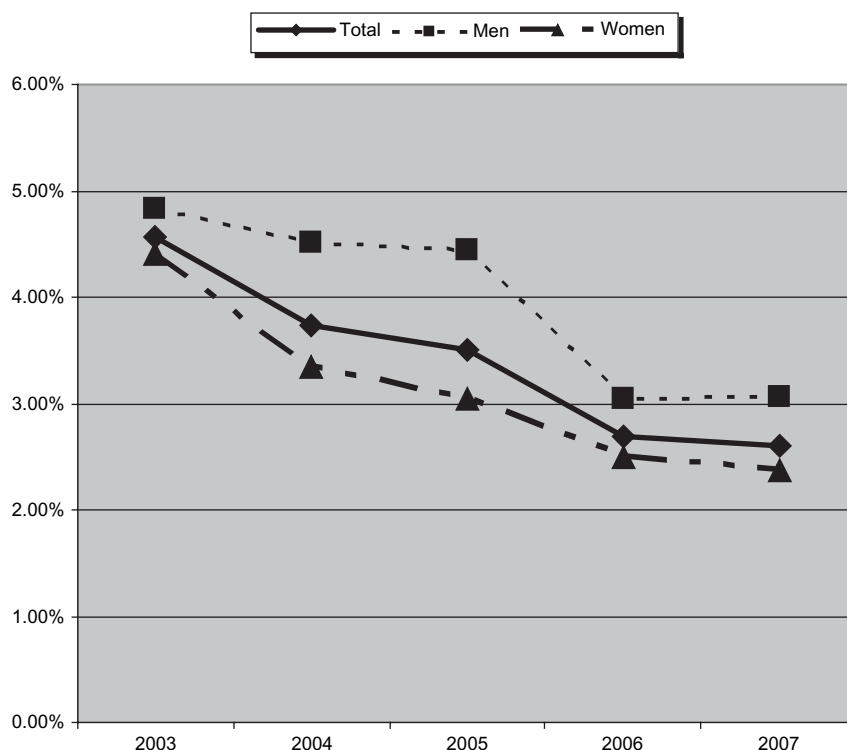


Fig. 1. Percentage of tested consecutive patients with a positive reaction to methyldibromo glutaronitrile in year 2003–2007.

listed as an ingredient or detected by chemical analysis of a product used by the patient decreased from 28.5% in 2003 to 3.0% in 2007 ($P < 0.001$) (Table 2).

Discussion

A significant decrease of contact allergy to MDBGN was found in both female and male eczema patients from 2003 to 2007. The decrease is because of reduced exposure.

In June 2002, the Scientific Committee on Cosmetic and Non-Food Products (SCC-NFP) (12), advisory to the EU Commission, adopted an opinion recommending the use of MDBGN restricted to rinse-off products because of the risk of contact allergy (12). This decision came into legal force on 24 September 2005 following agreement with the EU member states and was based, among others,

on epidemiological data showing a significant increase over a 10-year period in the frequency of contact allergy to MDBGN in European eczema patients (5). As a result of further experimental and epidemiological evidence showing that rinse-off products also caused contact allergy to MDBGN (6–8, 19, 20), the successor to the SCC-NFP, the Scientific Committee on Consumer Products (SCCP) adopted an opinion in March 2005 recommending that MDBGN should not be present in any cosmetic products (13). This opinion was accepted, and, from 22 June 2008, no cosmetic product made available to the European consumer may contain MDBGN. In 2003, 4.6% of patients tested in the network of the DCDG were allergic to MDBGN, which was even higher than the level of 3.5% positives found in 2000 in a European study (5). From 2003, a steady decrease in the rate of positive reactions was seen in the Danish network; in men, this was most pronounced from 2005. Scientific papers on the epidemic of contact allergy to MDBGN as well as the opinions adopted are likely to have influenced the use of MDBGN before regulations came into force. A Danish consumer organization, The Information Centre for Environment and Health, investigated the use of MDBGN in liquid soaps on the Danish market, following a public debate on the risk of allergy to MDBGN. In 2004, they found that 12 of 38 (27%) liquid soaps were

Table 2. Current relevance of MDBGN contact allergy

	Total number of MDBGN cases	Current relevance <i>n</i> (%)	MDBGN found in product <i>n</i> (%)
2003	158	81 (51.3)	45 (28.5)
2004	138	62 (44.9)	18 (13.0)
2005	147	52 (35.4)	9 (6.1)
2006	110	31 (28.2)	7 (6.4)
2007	100	29 (29.0)	3 (3.0)
Total	653	255 (39.0)	82 (12.0)

MDBGN, methyldibromo glutaronitrile.

preserved with MDBGN, while seven of 45 (15%) liquid soaps contained MDBGN in 2005 (21). Not only a significant decrease in positive patch test reactions to MDBGN has been seen but also a significant decrease in the proportion of patients from whom a positive patch test to MDBGN were of current relevance from 51.3% in 2003 to 29.0% in 2007 (Table 2). It seems that MDBGN has been removed from many products in Denmark. MDBGN was detected only in 3.0% of products used by MDBGN-positive patients in 2007. The British Contact Dermatitis Group also recently showed a significant decline in contact allergy to MDBGN comparing data from 2000 with those of 2004–2005 (22). It is likely that the same decreasing trend is also present in other EU countries. An update on the sensitivity to MDBGN and other preservatives in Europe after 2000 (5) would be of interest.

In conclusion, MDBGN has been the cause of an epidemic of allergic contact dermatitis. A significant decrease has been seen in the past 5 years following regulatory intervention. The decrease levelled off from 2006 to 2007, but MDBGN is still one of the most frequent allergens, although now with a low level of current relevance. The trends should be followed closely.

The interventions made have been simple and have had a major impact on the burden of allergic disease affecting the European citizen.

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