

diagnostic screening tool used most often, the fragrance mix (FM I), misses a considerable number of patients sensitized to fragrances. In a worldwide multicentre investigation, Larsen et al. identified several potentially allergenic fragrances and recommended further study (2, 3). 1 of them, Majantol® (Symrise, Holzminden, Germany) (CAS 103694-68-4), appears to be of particular interest (Fig. 1). Although classified as non-sensitizing according to predictive animal tests (Guinea Pig Maximization Test) (4), Larsen et al., by patch testing fragrance-sensitive volunteers in 2 studies ($n = 167$ and $n = 217$), detected a total of 16 cases allergic to Majantol 5% petrolatum (2, 3). In view of a lesser use of compounds of the FM I (5), substantiated by decreasing trends of sensitization (6), and in view of a probably increasing use of fragrances not to be labelled according to the EU legislation (7), such as Majantol, we were interested in the current frequency of sensitization to Majantol in an unselected, i.e. consecutively patch-tested population.

from the patients' history and clinical data are transferred to the data centre in Göttingen in an anonymous format. Majantol 5% in petrolatum, obtained from Hermal/Trolab, Reinbek, Germany, was patch tested in 6573 patients additionally to the standard series, i.e. in unselected patients, by departments joining the IVDK between July 2003 and June 2005. For the description of the demographic characteristics of the patients, the men, occupational-, atopic-, hand-, leg- and face dermatitis, Age ≥ 40 (MOAHLFA), index is used (9). Frequencies of sensitization (as per cent of patients tested) were calculated as crude proportions and as proportions standardized for sex and age (10). Patients allergic to Majantol were analysed for concomitant positive patch test reactions. The reaction index (RI) (11) and the positivity ratio (PR) (12) were calculated as parameters to further characterize the patch test preparation.

For data management and analysis, the statistical software package SAS (version 9.1, SAS Institute, Cary, NC, USA) was used.

Majantol® – a new important fragrance allergen

Contact Dermatitis 2007; 57: 48–50

Axel Schnuch¹, Johannes Geier¹,
Wolfgang Uter² and Peter J Frosch³

¹Information Network of Departments of Dermatology (IVDK), University of Göttingen, Göttingen, Germany,

²Department of Medical Informatics, Biometry and Epidemiology (IMBE), University of Erlangen-Nürnberg, Erlangen, Germany,

³Department of Dermatology, University of Witten/Herdecke and Klinikum Dortmund GmbH, Dortmund, Germany

Key words: contact allergy; fragrances; surveillance.

Contact allergy to fragrances is relatively frequent (1). However, the

Methods

The multicentre project IVDK (Information Network of Departments of Dermatology) is an instrument of epidemiological surveillance of contact allergy (8). Patch test results of every reading, as well as information

Results

Patch test results are presented in Table 1. With 40 doubtful or irritant and 36 allergic reactions (27 +, 7 ++ and 2 +++, i.e. 0.5% crude and standardized, 95% CI: 0.3–0.7%), the RI is –0.1 and the PR 75%. Patients

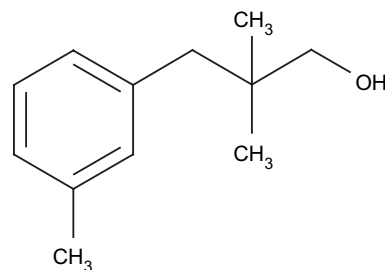


Fig. 1. Structure of the synthetic fragrance Majantol® (CAS 103694-68-4; $C_{12}H_{18}O$, synonym: benzenepropanol, beta,beta,3-trimethyl-; lily propanol, 2,2-dimethyl-3-(3-methylphenyl)propanol, 3-(2,2-dimethyl-3-hydroxypropyl)toluol).

Table 1. Frequencies of sensitization to majantol (5% petrolatum) in the total group and in women and men

	<i>n</i> test	Positive, <i>n</i> (%)	% positive standard	95% CI
Total	6573	36 (0.5)	0.5	0.3–0.7
Women	4089	26 (0.6)	0.6	0.3–0.8
Men	2484	10 (0.4)	0.3	0.1–0.5

Table 2. Concomitant reactions to fragrances in Majantol positive versus negative patients, sorted in decreasing order of the crude percentage of positive reactions

Allergens	Majantol positive				Majantol negative	
	Tested, <i>n</i>	Positive, <i>n</i> (%)	% positive standard	95% CI	% positive standard	95% CI
Tree moss absolute	12	6 (50.0)	40.7	4.5–76.9	2.4	1.7–3.1
Ylang-Ylang (I + II)	12	6 (50.0)	40.7	4.5–76.9	2.2	1.6–2.9
Balsam of Peru (<i>Myroxylon pereirae</i> resin)	36	14 (38.9)	31.3	15.0–47.6	6.6	6.0–7.2
Amly cinnamic alcohol	11	4 (36.4)	30.2	0.0–64.5	0.1	0.0–0.2
Oakmoss absolute	15	5 (33.3)	42.3	16.0–68.6	2.5	1.9–3.1
Fragrance-mix II	12	4 (33.3)	60.5	45.9–75.1	4.2	3.3–5.2
Fragrance-mix	36	10 (27.8)	40.3	24.7–56.0	6.6	5.9–7.2
Colophony	36	10 (27.8)	27.9	11.8–44.1	4.5	3.9–5.0
Eugenol	15	4 (26.7)	18.0	1.7–34.3	0.5	0.2–0.9
Compositae mix	36	9 (25.0)	22.5	7.0–38.0	2.1	1.7–2.5
Alpha amyl cinnamic aldehyde	15	3 (20.0)	14.0	0.0–29.4	0.1	0.0–0.3
Oil of turpentine	36	6 (16.7)	17.3	2.7–32.0	1.4	1.1–1.7
Hydroxycitronellal	15	2 (13.3)	9.9	0.0–23.8	1.8	1.2–2.4
Propolis	36	4 (11.1)	6.8	0.4–13.3	2.0	1.7–2.4
HMPCC	36	4 (11.1)	26.5	14.8–38.2	2.0	1.6–2.3

HMPCC, hydroxymethylpentylcyclohexene carboxaldehyde (e.g. LyrallTM); % positive standard, CI, proportion standardized for age and sex, and the respective confidence intervals.

Note that some allergens were only tested in a limited number of patients. Patients testing negative to Majantol for comparison – in case CIs do not overlap, there is a significant difference.

reacting positively to Majantol compared with non-allergic controls were older (80.6% versus 69.8% age 40 and above), with less hand dermatitis (13.9% versus 27.5%) and less occupational dermatitis (8.3% versus 14.3%), but more leg dermatitis (27.8% versus 12.7%). With regard to other items of the MOAHLFA-index, the groups did not differ much. The most frequent concomitant reactions (many significantly more frequent than in patients not positive to Majantol) are presented in Table 2.

Discussion

The field of contact allergy to fragrances is subject to continuous changes. After a steep increase in sensitization rates to substances of the FM I during the late 90s and a significant decrease during the following years (6), the limited sensitivity of the FM I as a screening agent for fragrance contact allergy became apparent and further fragrance compounds considered important were combined in the FM II. Testing the FM II showed sensitization frequencies of more than 4% in a European (13) and a German study (14). Furthermore, the EU decided that if consumer products contain 1 or several fragrances out of a list of 26 fragrances considered as contact allergens, these fragrances should be labelled (7). However, Majantol® was not mentioned in this list.

In this study, we found a sensitization frequency of 0.5% (Table 1), which is comparable, for example, with eugenol (15). There were 9 stronger (++) reactions, but the negative RI (–0.1) is indicative of a substantial number of irritant reactions. Patients sensitized to Majantol were older, and leg dermatitis was more frequent. Higher age and leg dermatitis were generally identified as risk factors for sensitization to fragrances (16), not only to those of the FM I (15). Interestingly, in a smaller study (*n* = 167) by Larsen et al., all 9 patients reacting to Majantol were older than 40 years (2).

Analysis of concomitant reactions in Majantol-sensitized patients showed that only 10/36 (28%) reacted to the FM I, 4/12 to the FM II and even less to Lyrall® (4/36 = 11%). In contrast, reactions to Tree moss and Ylang-Ylang (each 6/12) and balsam of Peru (*Myroxylon pereirae* resin, 14/36 = 39%) were quite frequent. High frequencies of concomitant reactions are probably because of coexposure. One may speculate if the surprisingly low concordance with Lyrall® (Table 2) indicates that both fragrances with a floral note are not often used together.

Conclusions

1. Majantol is a relatively frequent fragrance allergen comparable with a number of well known other fragrances (15).

2. Sensitization to Majantol is neither detected by the FM I nor by the FM II. It should therefore be included in a cosmetic or fragrance series.
3. The divergence between predictive animal tests and human observation stresses the need for epidemiological surveillance in postmarketing risk assessment (17).
4. EU regulation politics on fragrances should accordingly be adapted (7). As part of the industry obviously circumvents current regulation by switching to ingredients, which are not regulated, yet possibly problematic, authorities and the cosmetic industry should consider the impact of regulation and unwanted consequences, respectively, under the issue of the 'substitute problem'.

References

1. Schnuch A, Uter W, Geier J, Gefeller O. Epidemiology of contact allergy: an estimation of morbidity employing the clinical epidemiology and drug utilisation research (CE-DUR) approach. *Contact Dermatitis* 2002; 47: 32–39.
2. Larsen W, Nakayama H, Lindberg M et al. Fragrance contact dermatitis: a worldwide multicenter investigation (part I). *Am J Contact Derm* 1996; 7: 77–83.
3. Larsen W, Nakayama H, Fischer T et al. Fragrance contact dermatitis – a worldwide multicenter investigation (part III). *Contact Dermatitis* 2002; 46: 141–144.

4. Majantol (R) Safety data sheet 1997. Clifton, NJ: Fragrance Resources Inc.
5. Rastogi S C, Menne T, Johansen J D. The composition of fine fragrances is anonymous changing. *Contact Dermatitis* 2003; 48: 130–132.
6. Schnuch A, Lessmann H, Geier J, Frosch P J, Uter W. Contact allergy to fragrances: frequencies of sensitization from 1996 to 2002. Results of the IVDK. *Contact Dermatitis* 2004; 50: 65–76.
7. Directive 2003/15/EC of the European Parliament and of the Council of 27 February 2003 amending Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products. *Official Journal of the European Union* 2003; L66: 26–35.
8. Uter W, Schnuch A, Geier J, Frosch P J. Epidemiology of contact dermatitis: the information network of the departments of dermatology (IVDK) in Germany – a surveillance system on contact allergies. *Eur J Dermatol* 1998; 8: 36–40.
9. Schnuch A, Geier J, Uter W et al. National rates and regional differences in sensitization to allergens of the standard series. Population adjusted frequencies of sensitization (PAFS) in 40.000 patients from a multicenter study (IVDK). *Contact Dermatitis* 1997; 37: 200–209.
10. Schnuch A. PAFS – Population adjusted frequency of sensitization (I) – Influence of sex and age. *Contact Dermatitis* 1996; 34: 377–382.
11. Brasch J, Geier J, Henseler T. Evaluation of patch test results by use of the reaction index – an analysis of data recorded by the Information Network of Departments of Dermatology (IVDK). *Contact Dermatitis* 1995; 33: 375–380.
12. Geier J, Uter W, Lessmann H, Schnuch A. The positivity ratio – another parameter to assess the diagnostic quality of a patch test preparation. *Contact Dermatitis* 2003; 48: 280–282.
13. Frosch P J, Pirker C, Rastogi S C et al. Patch testing with a new fragrance mix detects additional patients sensitive to perfumes and missed by the current fragrance mix. *Contact Dermatitis* 2005; 52: 207–215.
14. Geier J, Lessmann H, Uter W, Schnuch A. Experiences with the fragrance mix II – the German perspective. *Contact Dermatitis* 2006; 55(Suppl. 1): 12.
15. Schnuch A, Geier J, Uter W, Frosch P J. Sensitization to 26 fragrances regulated by the European Commission. *Contact Dermatitis* 2007; 57: 1–10.
16. Uter W, Schnuch A, Geier J, Pfahlerberg A, Gefeller O. Association between occupation and contact allergy to the fragrance mix: a multi-factorial analysis of national surveillance data. *Occup Environ Med* 2001; 58: 392–398.
17. Menné T, Wahlberg J E. Risk assessment failures of chemicals commonly used in consumer products. *Contact Dermatitis* 2002; 46: 189–190.

Address:

Professor Dr med. Axel Schnuch
 Zentrale des IVDK
 Universitäts-Hautklinik
 Von Siebold Str. 3
 Göttingen
 Germany
 Tel: +49 551 39 64 39
 Fax: +49 551 39 60 95
 e-mail: aschnuch@med.uni-goettingen.de