

Prevalence of fragrance contact allergy in the general population of five European countries: a cross-sectional study*

T.L. Diepgen,¹ R. Ofenloch,¹ M. Bruze,² S. Cazzaniga,³ P.J. Coenraads,⁴ P. Elsner,⁵ M. Goncalo,⁶ Å. Svensson⁷ and L. Naldi³

¹Department of Social Medicine, Occupational and Environmental Dermatology, University Hospital Heidelberg, Thibautstraße 3, 69115 Heidelberg, Germany

²Department of Occupational and Environmental Dermatology, University Hospital Malmö, S-20502 Malmö, Sweden

³Department of Dermatology, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Centro Studi GISED – FROM Presidio Ospedaliero Matteo Rota, Via Garibaldi 13/15, 24122 Bergamo, Italy

⁴Occupational and Environmental, Dermatology Unit, State University Hospital, P.O. Box 30.001, NL-9700 RB Groningen, the Netherlands

⁵Klinik für Dermatologie und dermatologische Allergologie, Klinikum der FSU Jena, Erfurter Str. 35, D-07740, Jena, Germany

⁶Clinica de Dermatologia, Hospital da Universidade Praceta Motal Pinto, Rua Infanta D.Maria, n 30-A-3D, P-3000-075, Coimbra, Portugal

⁷Department of Dermatology, University Hospital Malmö, S-20502 Malmö, Sweden

Linked Comment: Uter, *Br J Dermatol* 2015; **173**: 1358–59

Summary

Correspondence

Thomas L. Diepgen.

E-mail: thomas.diepgen@med.uni-heidelberg.de

Accepted for publication

21 August 2015

Funding sources

This study was supported by the Research Institute for Fragrance Materials, Inc.

Conflicts of interest

M.B. is a member of REXPAN, an independent expert panel to the Research Institute for Fragrance Materials, Inc.

*Plain language summary available online

DOI 10.1111/bjd.14151

Background Contact allergy to fragrances is assessed mostly in clinical populations of patients. Studies in the general population are scarce and vary in their methodology across countries.

Objectives To determine the prevalence of fragrance contact allergy in the European general population and to assess the clinical relevance of positive patch test reactions to different fragrances.

Methods In five European countries (Germany, Italy, the Netherlands, Portugal and Sweden) a random sample from the general population aged 18–74 years was drawn. In total, 12 377 subjects were interviewed in this cross-sectional study and a random sample ($n = 3119$) was patch tested using the TRUE Test and Finn Chamber techniques. Patch test procedures were harmonized by mandatory training before the study and monitoring during the study.

Results The highest prevalence for contact allergy of 2.6% [95% confidence interval (CI) 2.1–3.2] was found for fragrance mix (FM) I in petrolatum, with a high content of atranol and chloratranol, followed by 1.9% (95% CI 1.5–2.4) for FM II in petrolatum. The conservatively estimated prevalence of fragrance contact allergy was 1.9% (95% CI 1.5–2.5). This is defined as the existence of a positive patch test to FM I or FM II; any of their individual materials; Myroxylon pereirae; sesquiterpene lactones or 3- and 4-hydroxyisohexyl 3-cyclohexene carboxaldehyde that show clinical relevance, defined conservatively as lifetime avoidance of scented products and an itchy skin rash lasting > 3 days in a lifetime. Using the reported lifetime prevalence of any contact dermatitis instead of the lifetime prevalence of any itchy skin rash, the prevalence is 0.8% (95% CI 0.5–1.2). The prevalence rates of contact allergy to fragrances in women are about twice those in men.

Conclusions This study helps to identify targets for prevention of fragrance allergy.

What's already known about this topic?

- Contact allergy to fragrances is very common, and a prevalence rate of up to 14% has been reported in studies of clinical populations.
- Studies in the general population are scarce and vary in their methodology across countries.

What does this study add?

- We report the prevalence of contact allergy to fragrance mix (FM) I and FM II and avoidance of scented products in five European countries.
- High avoidance rates of scented products due to skin complaints were reported for leave-on, rinse-off, and household or functional products.
- The highest prevalence for contact allergy (2.6%) was found for FM I in petrolatum, followed by 1.9% for FM II in petrolatum, with a higher prevalence in women.
- There was no statistically significant difference for contact allergy to the different fragrance allergens between countries.

Contact allergy to fragrances is assessed mostly in clinical populations of dermatological patients.¹ Studies in the general population are scarce and vary in their methodology across countries.¹ The objectives of our study were to determine the prevalence of contact allergy in the European general population, with a special focus on fragrance allergy, and to assess the clinical relevance of positive patch test reactions to different fragrance markers.

In a recent manuscript we assessed reliable estimates of the prevalence rates of contact allergy to common allergens in the general population in Europe and evaluated the lifetime prevalence of different skin diseases.² This paper is the second presenting the patch test data on fragrance contact allergy, and the third in a series of papers on this large prevalence study, which was conducted in Europe.³ Population-based epidemiological studies on contact allergy and allergic contact dermatitis are needed to provide important risk data to government agencies, industries and consumer-oriented groups.²

Materials and methods

Study design

The study design, including sample-size calculation and data collection, has been published previously.^{3,4} Briefly, the EDEN Fragrance Study was a cross-sectional epidemiological study conducted in several European regions, including the metropolitan areas of Malmö (Sweden), Jena (Thüringen, Germany) and Heidelberg (Baden-Württemberg, Germany), and the provinces of Groningen (the Netherlands), Bergamo (Italy) and Coimbra (Portugal). A random sample was selected from the general population, based on electoral precincts, aged 18–74 years.³ The study followed a stratified, proportional sampling with replacement design as described previously.⁴ In total, 12 377 subjects were interviewed with a standardized questionnaire, and a random sample ($n = 3119$) was patch tested to investigate sensitization to various allergens. The interview data were published recently;³ here we present the patch test data for different fragrance allergens. The full phase of the study started in August 2008 and ended in October 2011. Less than 1% of

the participants refused to be patch tested. The study was approved by the ethics committee of each participating centre.

Patch testing

The patch test procedure and its high standardization, has been published previously.^{2,4} The recent recommendations on how to improve the quality of multicentre patch test studies were followed.⁵ Patch testing was performed according to the International Contact Dermatitis Research Group guidelines.⁶ Weak (+), strong (++) and extreme (+++) reactions with an allergic morphology are considered positive reactions (Appendix S1; see Supporting Information).

Data collection

As reported previously, the interview was conducted face-to-face with a trained interviewer and consisted of three parts.^{3,4} The first part recorded demographic and personal characteristics. The second part recorded any history of skin problems, including localized erythema or itchy skin rashes that lasted > 3 days during the last month or the last year (including the last month), or that occurred over the respondent's lifetime (including the last month and the last year). The third part comprised a detailed history of exposure to consumer products of common use, including the following: (i) toiletry items that remained on the skin or were rinsed off; (ii) household and other functional items (e.g. cleaning and freshener products); (iii) adornments (e.g. metals, leather, piercing and jewellery, and temporary and permanent tattoos); and (iv) protective products (e.g. plastics and rubber products, bandages or tapes). Participants were also asked to list any topical medication used and any history of adverse reactions. For each product, they reported the frequency of use and history of avoidance because of skin problems.

Fragrance allergy and its clinical relevance

A clinically relevant patch test reaction was defined as follows: positive patch test (+/++/+++ reactions) to a fragrance allergen in a subject who also reported a lifetime history of avoidance

of any scented product because of any skin problem plus an itchy skin rash lasting > 3 days on any site of the body during the lifetime. As well as an itchy skin rash lasting > 3 days we also used the reported lifetime prevalence of contact dermatitis (allergic and/or irritant) to establish the clinical relevance of a contact allergy to fragrance allergens.

Fragrance contact allergy was defined according to two different approaches. Firstly, the 'conservative' approach of fragrance contact allergy was defined as a positive patch test to either fragrance mix (FM) I in the TRUE Test (SmartPractice, Phoenix, AZ, U.S.A.), containing *Evernia prunastri* (oak moss) with a high content of atranol and chloratranol; fragrance mix II (FM II); *Myroxylon pereirae* (MP) or sesquiterpene lactones. Secondly, as many patch test clinics do not patch test the constituents of FM I or FM II unless FM I or FM II shows a positive reaction, the second approach was defined by the existence of a positive patch test to FM I in the TRUE Test or FM II, and a positive reaction to either the constituents of FM I or FM II, MP, sesquiterpene lactones or hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC). This is called the 'clinical' approach to fragrance allergy.

Sample size and data analyses

The sample-size calculation has been described previously.⁴ All statistical analyses were performed using SPSS 20 (IBM,

Armonk, NY, U.S.A.). Descriptive data are presented as numbers and relative frequencies, for demographics and skin complaints of individuals. The prevalences of patch test reactions to different allergens are expressed as numbers and relative frequencies, together with the 95% confidence intervals (CIs). In order to compare prevalence across countries, the prevalences were also calculated by country using age-standardized estimates. A P-value < 0.01 was considered statistically significant. Age standardization was performed according to the direct method.⁷

Results

Avoidance of scented products due to skin complaints

Table 1 shows the reported rates of avoidance of different products among the 12 377 interviewed subjects compared with the 3119 subjects patch tested. The prevalence rates among the 12 377 subjects interviewed are very similar to those of the 3119 subjects patch tested. The highest avoidance was reported for scented products intended to be left on the skin (37.0% of the interviewed subjects vs. 37.4% of the patch-tested subjects), with the highest avoidance rates for deodorants or antiperspirants (17.1% in both groups) followed by skin creams, lotions etc. (12.1% and 10.3%, respectively) and eye make-up products (9.1% and 9.0%).

Table 1 Reported avoidance of scented products among 3119 subjects patch tested compared with the 12 377 interviewed subjects^a in six European regions

	Prevalence sample (N = 12 377) ^a		Subsample patch tested (N = 3119)	
	n	% (95% CI)	n	% (95% CI)
Products intended to be left on the skin	4580	37.0 (36.0–37.8)	1166	37.4 (35.6–39.1)
Perfumes, liquid toiletries or other highly perfumed products	967	8.0 (7.5–8.5)	236	7.8 (6.9–8.9)
Men's cologne, aftershaves etc.	560	4.8 (4.4–5.2)	126	4.3 (3.6–5.0)
Sunscreens	732	6.1 (5.6–6.5)	160	5.3 (4.5–6.2)
Skin creams, lotions etc.	1469	12.1 (11.6–12.7)	312	10.3 (9.2–11.4)
Deodorants or antiperspirants	2079	17.1 (16.4–17.8)	523	17.1 (15.8–18.4)
Hair-care products (sprays, tonics, gels, mousses – not shampoos, conditioners or other rinse-off products)	552	4.6 (4.2–5.0)	141	4.7 (4.0–5.5)
Eye make-up products	1066	9.1 (8.6–9.7)	263	9.0 (8.0–10.0)
Lipsticks and lip balms	364	3.1 (2.8–3.4)	82	2.8 (2.2–3.3)
Other cosmetic products (foundation, blushes, powders etc.)	554	4.8 (4.4–5.2)	129	4.4 (3.7–5.1)
Personal hygiene products (sanitary napkins, tampons etc.)	673	5.7 (5.3–6.2)	194	6.6 (5.6–7.6)
Products intended to be rinsed off, excluding hair colorants	2605	21.0 (20.4–21.8)	607	19.5 (18.1–20.8)
Bath oils, salts, beads etc.	641	5.4 (5.0–5.9)	127	4.4 (3.6–5.2)
Bar soaps, liquid soaps, waterless hand cleansers etc.	1020	8.3 (7.8–8.8)	231	7.5 (6.6–8.4)
Shampoos, cream rinses, conditioners etc.	1220	10.0 (9.4–10.4)	286	9.3 (8.3–10.6)
Shaving products	691	5.9 (5.5–6.3)	169	5.7 (4.9–6.6)
Mouthwashes or toothpastes	249	2.0 (1.8–2.3)	59	1.9 (1.2–2.4)
Household or functional products	2188	17.7 (17.0–18.4)	512	16.4 (15.1–17.8)
Laundry detergents, softeners etc.	1079	9.0 (8.4–9.5)	246	8.2 (7.2–9.0)
Liquid dishwashing detergents	866	7.1 (6.7–7.6)	225	7.4 (6.5–8.3)
Scouring powders, hard surface cleaners etc.	1050	8.8 (8.2–9.3)	244	8.1 (7.1–9.1)
Air fresheners, aerosol or liquid (including wicks)	240	2.0 (1.8–2.3)	52	1.8 (1.3–2.3)
Carpet shampoos, fresheners etc.	82	1.0 (0.9–1.2)	34	1.2 (0.8–1.6)

CI, confidence interval. ^aPreviously reported by Naldi *et al.*³

Perfumes, liquid toiletries and other highly perfumed products were reported to be avoided because of any skin complaints by 8.0% of the interviewed subjects and 7.8% of the patch-tested subjects.

The reported avoidance of rinse-off products, excluding hair colorants, was 21.0% in the interviewed subjects and 19.5% in the patch-tested subjects, with the highest rates for shampoos, cream rinses, conditioners etc. followed by bar soaps, liquid soaps, waterless hand cleansers etc. The reported avoidance for household or functional products was 17.7% in the interviewed subjects and 16.4% in the patch-tested subjects, with the highest rates for laundry detergents, softeners etc. followed by scouring powders, hard surface cleaners etc. and liquid dishwashing detergents.

Contact allergy to different patch-tested fragrance allergens

Independently of the patch test technique, the European baseline patch test series is expected to test an FM I with a high content of atranol and chloratranol. This is why only the results of testing with such preparations of FM I are presented in this paper. The results of patch testing with the *E. prunastri* preparations with a low content of atranol and chloratranol are presented elsewhere (Bruze *et al.*, in press).

Table 2 shows the prevalence of contact allergy, defined as at least one positive patch test reaction (+/++/+++) to different

fragrance markers. In addition, the strengths of the reactions (+/++/+++) in the patch test are given. The majority of the positive reactions to all fragrance allergens were diagnosed as weak (+) reactions, and only a few extreme reactions (+++) were seen. All prevalence estimates were higher in women than in men. The highest prevalence for contact allergy [2.6% (95% CI 2.1–3.2)] was found for FM I in petrolatum with a high content of atranol and chloratranol, which was higher than the TRUE Test preparation of FM I with a high content of atranol and chloratranol. Out of 50 subjects with at least one positive patch test reaction (+/++/+++) to the TRUE Test preparation with FM I, 37 (74%) also reacted to FM I in petrolatum, and out of 74 subjects with at least one positive patch test reaction (+/++/+++) to FM I in petrolatum, 37 (50%) also reacted to the TRUE Test preparation with FM I.

The highest prevalence for an ingredient was seen for *E. prunastri* 2% with high atranol and chloratranol (prevalence 1.0%, 95% CI 0.7–1.4), followed by isoeugenol 2% (prevalence 0.7%, 95% CI 0.4–1.0). The prevalence for *E. prunastri* 2% with low atranol and chloratranol was 0.5% (95% CI 0.3–0.8).

The prevalence of contact allergy to FM II in petrolatum was 1.9% (95% CI 1.5–2.4), with a higher prevalence in women (2.5%) than in men (1.3%). Of the six constituents of FM II, HICC, which was tested at 5.0% w/w, had the highest prevalence with 1.5% (95% CI 1.1–1.9). Contact allergy to sesquiterpene lactone mix was found in 0.1% (95% CI 0.0–0.2) and to MP in 0.7% (95% CI 0.4–1.0).

Table 2 Prevalence rates of contact allergy (defined as at least one positive reaction in the patch test) of different fragrances by sex and in total (3119 patch-tested subjects)

	+	++	+++	Total (N = 3119) ^b		Male (N = 1405)		Female (N = 1712)	
				n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
FM I TRUE Test ^a (high atranol and chloratranol)	27	20	3	50	1.8 (1.4–2.3)	16	1.3 (0.8–2.0)	34	2.3 (1.6–3.1)
FM I Finn Chamber (high atranol and chloratranol)	45	29	8	82	2.6 (2.1–3.2)	29	2.1 (1.3–2.3)	53	3.1 (2.4–4.1)
Cinnamyl alcohol 2%	6	4	0	10	0.3 (0.1–0.5)	0	0.0 (0.0–0.2)	10	0.6 (0.3–1.0)
Cinnamal 1%	16	10	0	26	0.8 (0.5–1.2)	7	0.5 (0.1–0.9)	19	1.1 (0.6–1.6)
Amylcinnamyl alcohol 2%	2	1	0	3	0.1 (0.0–0.2)	0	0.0 (0.0–0.2)	3	0.2 (0.0–0.4)
Geraniol 2%	11	2	0	13	0.4 (0.2–0.7)	5	0.4 (0.1–0.7)	8	0.5 (0.2–0.8)
Hydroxycitronellal 2%	12	2	1	15	0.5 (0.3–0.7)	3	0.2 (0.0–0.4)	12	0.7 (0.3–1.1)
Eugenol 2%	6	0	0	6	0.2 (0.1–0.4)	3	0.2 (0.0–0.5)	3	0.2 (0.0–0.4)
Isoeugenol 2%	13	6	2	21	0.7 (0.4–1.0)	8	0.6 (0.2–1.0)	13	0.8 (0.4–1.2)
<i>Evernia prunastri</i> 2%	11	5	0	16	0.5 (0.3–0.8)	5	0.4 (0.1–0.7)	11	0.6 (0.3–1.1)
<i>Evernia prunastri</i> 2% (high atranol and chloratranol)	19	9	4	32	1.0 (0.7–1.4)	14	1.0 (0.5–1.6)	18	1.1 (0.6–1.5)
Sorbitan sesquiolate 20%	2	1	1	4	0.1 (0.0–0.3)	1	0.1 (0.0–0.2)	3	0.2 (0.0–0.4)
FM II Finn Chamber	34	21	5	60	1.9 (1.5–2.4)	18	1.3 (0.7–1.9)	42	2.5 (1.7–3.3)
Citral 2%	4	2	0	6	0.2 (0.1–0.4)	2	0.1 (0.0–0.4)	4	0.2 (0.0–0.5)
Citronellol 1%	2	1	0	3	0.1 (0.0–0.2)	0	0.0 (0.0–0.2)	3	0.2 (0.0–0.5)
Coumarin 5%	2	1	0	3	0.1 (0.0–0.2)	1	0.1 (0.0–0.2)	2	0.1 (0.0–0.4)
Farnesol 5%	13	1	0	14	0.4 (0.2–0.7)	3	0.2 (0.0–0.4)	11	0.6 (0.3–1.0)
Hexylcinnamal 10%	6	1	1	8	0.3 (0.1–0.4)	2	0.1 (0.0–0.4)	6	0.4 (0.1–0.7)
HICC 5%	27	12	7	46	1.5 (1.1–1.9)	12	0.9 (0.4–1.4)	33	1.9 (1.3–2.6)
Sesquiterpene lactone mix 0.1%	2	0	1	3	0.1 (0.0–0.2)	1	0.1 (0.0–0.2)	2	0.1 (0.0–0.3)
<i>Myroxylon perei</i>	18	3	2	23	0.7 (0.4–1.0)	6	0.4 (0.1–0.8)	17	1.0 (0.6–1.5)

CI, confidence interval; FM, Fragrance mix; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde. ^aTested in only 2740 subjects. ^bMissing sex data for two subjects.

Not all subjects who had a positive patch test reaction (+/++/+++) to the different fragrance mixes also reacted positively (+/++/+++) to at least one of the corresponding single constituents of that fragrance mix, and vice versa (Table 3). Out of 50 subjects positive to the TRUE Test preparation with FM I with a high content of atranol and chloratranol, 28 (56%) also reacted to at least one of the single constituents of FM I, and out of 69 subjects positive to at least one of the single constituents of FM I, only 27 (39%) also reacted to FM I TRUE Test preparation (FM I TRUE Test

preparation patch tested in 2740 subjects only). However, out of 82 subjects positive to FM I in petrolatum, 52 (63%) also reacted to at least one of the single constituents of FM I, and out of 86 subjects positive to a single constituents of FM I, 52 (60%) also reacted to FM I in petrolatum. Out of 60 subjects positive to FM II, 50 (83%) also reacted to a single substance of FM II, and out of 72 subjects positive to a single substance of FM II, 50 (69%) also reacted to FM II. There was a strong relationship between the strength of the reaction to the different FMs and the number of positive reactions to at least one of the single constituents of the corresponding FM, and vice versa.

Out of 3119 patch-tested subjects, 140 (4.5%) had a positive reaction to at least one ingredient of FM I or FM II, 100 (3.2%) to only one substance, 33 (1.1%) to two substances and seven (0.2%) to more than two substances.

In Table 4, the age-standardized prevalences of contact allergy to the different fragrance allergens and sesquiterpene lactone mix in the different European countries are presented. There was no statistically significant difference for contact allergy to the different fragrance allergens between the different countries.

Clinical relevance: avoidance of scented products

We analysed rates of avoidance of scented products due to skin complaints and itchy skin rash lasting > 3 days in a lifetime in subjects with contact allergy to different fragrance allergens. The results are presented in Table 5. Of those 82 subjects with a positive patch test reaction to FM I in petrolatum with a high content of atranol and chloratranol (prevalence 2.6%, 95% CI 2.1–3.2), 53 also reported the avoidance of scented products due to skin problems during their lifetime (prevalence 1.7%, 95% CI 1.3–2.2), and 42 subjects reported an itchy skin rash lasting > 3 days in their lifetime (prevalence 1.3%, 95% CI 0.9–1.8). Of those 60 subjects with a contact allergy to FM II (prevalence 1.9%, 95% CI 1.4–2.5), 41 also reported the avoidance of scented products due to skin problems in their lifetime (prevalence 1.3%, 95% CI 0.9–1.7), and 29 subjects reported an itchy skin rash lasting > 3 days in their lifetime (prevalence 0.9%, 95% CI 0.6–1.3). On average, about half of those subjects with a contact allergy to any of the tested fragrance allergens had a clinically relevant reaction according to the algorithm used.

Fragrance contact allergy defined according to the 'conservative' approach was diagnosed in 4.1% of patients (95% CI 3.4–4.9), and in 1.9% (95% CI 1.5–2.5) this was clinically relevant. If we use the reported lifetime prevalence of any contact dermatitis instead of the lifetime prevalence of any itchy skin rash, the prevalence is 0.8% (95% CI 0.5–1.2) (24 of 113 subjects).

Fragrance contact allergy defined according to the 'clinical' approach was diagnosed in 2.1% of participants (95% CI 1.6–2.7), and it was clinically relevant in 1.2% (95% CI 0.8–1.6). If we use the reported lifetime prevalence of contact dermatitis

Table 3 Relationship between the strength of reaction to different fragrance mixes (FMs) and the number of reactions to at least one of the ingredients of the corresponding FM, and vice versa

Strength of patch test reaction	Number of subjects	Number (%) of subjects with concomitant reactions to at least one ingredient of the corresponding FM		
		+ / ++ / +++	Irr / ?	Negative
FM I TRUE Test preparation ^a				
+	27	12 (44)	2	13
++	20	13 (65)	2	5
+++	3	3 (100)	—	—
All	50	28 (56)	4	18
FM I petrolatum				
+	45	24 (53)	6	15
++	29	21 (72)	3	5
+++	8	7 (88)	—	1
All	82	52 (63)	9	21
FM II				
+	34	26 (76)	4	4
++	21	19 (90)	—	2
+++	5	5 (100)	—	—
All	60	50 (83)	4	6

		Number (%) of subjects with concomitant reactions to the corresponding FM		
		+ / ++ / +++	Irr / ?	Negative
FM I TRUE Test preparation ^a				
Ingredients of FM I ^a				
+	48	12 (25)	7	29
++	18	12 (67)	—	6
+++	3	3 (100)	—	—
All	69	27 (39)	7	35
FM I petrolatum				
Ingredients of FM I				
+	59	29 (49)	8	22
++	23	19 (83)	1	3
+++	4	4 (100)	—	—
All	86	52 (60)	9	25
FM II				
Ingredients of FM II				
+	48	29 (60)	7	12
++	17	14 (82)	1	2
+++	7	7 (100)	—	—
All	72	50 (69)	8	14

^aTested in only 2740 subjects.

Table 4 Age-standardized prevalence rates of contact allergy (defined as at least one positive reaction in the patch test) of different fragrances by country

	Germany (N = 1024)		Italy (N = 546)		The Netherlands (N = 500)		Portugal (N = 531)		Sweden (N = 518)		Total (N = 3119) ^b	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
FM I TRUE Test ^a (high atanol and chloratranol)	21	2.4 (1.4–3.4)	8	1.5 (0.5–2.6)	6	1.8 (0.4–3.2)	6	1.2 (0.2–2.0)	9	2.3 (0.8–3.7)	51	1.9 (1.4–2.4)
FM I Finn Chamber (high atanol and chloratranol)	32	3.1 (2.1–4.2)	12	2.2 (1.0–3.4)	11	2.2 (0.9–3.5)	15	2.8 (1.4–4.2)	13	2.6 (1.2–3.9)	83	2.7 (2.1–3.2)
Cinnamyl alcohol 2%	2	0.2 (0.0–0.5)	3	0.6 (0.0–1.3)	1	0.2 (0.0–0.5)	2	0.4 (0.0–0.9)	2	0.4 (0.0–0.9)	10	0.3 (0.1–0.5)
Cinnamal 1%	10	1.0 (0.4–1.5)	4	0.8 (0.0–1.5)	3	0.7 (0.0–1.3)	7	1.3 (0.3–2.3)	3	0.6 (0.0–1.3)	28	0.9 (0.5–1.2)
Amylcinnamyl alcohol 2%	2	0.2 (0.0–0.5)	0	0.0 (0.0–0.5)	0	0.0 (0.0–0.6)	0	0.0 (0.0–0.6)	1	0.1 (0.0–0.4)	3	0.1 (0.0–0.2)
Geraniol 2%	5	0.5 (0.01–0.9)	0	0.0 (0.0–0.5)	1	0.3 (0.0–0.6)	4	0.8 (0.3–2.3)	2	0.4 (0.0–0.8)	12	0.4 (0.2–0.6)
Hydroxycitronellal 2%	8	0.8 (0.2–1.3)	1	0.1 (0.0–0.5)	4	0.9 (0.0–1.6)	1	0.2 (0.0–0.5)	1	0.2 (0.0–0.6)	15	0.5 (0.3–0.7)
Eugenol 2%	4	0.4 (0.0–0.8)	0	0.0 (0.0–0.5)	1	0.3 (0.0–0.6)	0	0.0 (0.0–0.6)	1	0.1 (0.0–0.4)	6	0.2 (0.0–0.4)
Isoeugenol 2%	9	0.9 (0.3–1.4)	3	0.6 (0.0–1.2)	2	0.4 (0.0–0.7)	5	1.0 (0.1–1.7)	1	0.2 (0.0–0.6)	21	0.7 (0.4–1.0)
Evernia prunastri 2%	10	1.0 (0.4–1.5)	1	0.1 (0.0–0.5)	2	0.5 (0.0–1.0)	3	0.6 (0.0–1.2)	0	0.0 (0.0–0.6)	16	0.5 (0.3–0.7)
Evernia prunastri 2% (high atanol and chloratranol)	15	1.4 (0.7–2.1)	1	0.1 (0.0–0.5)	6	1.1 (0.2–2.0)	5	1.0 (0.1–1.7)	8	1.5 (0.4–2.5)	34	1.1 (0.7–1.4)
Sorbitan sesquiolate 20%	0	0.0 (0.0–0.3)	1	0.1 (0.0–0.5)	2	0.4 (0.0–0.9)	0	0.0 (0.0–0.6)	1	0.1 (0.0–0.4)	3	0.1 (0.0–0.2)
FM II Finn Chamber	33	3.2 (2.1–4.3)	7	1.3 (0.3–2.2)	5	1.0 (0.1–1.9)	8	1.5 (0.4–2.5)	9	1.9 (0.6–3.0)	63	2.0 (1.5–2.5)
Citral 2%	3	0.3 (0.0–0.6)	0	0.0 (0.0–0.5)	1	0.2 (0.0–0.5)	0	0.0 (0.0–0.6)	1	0.2 (0.0–0.6)	5	0.2 (0.0–0.3)
Citronellol 1%	1	0.1 (0.0–0.3)	0	0.0 (0.0–0.5)	1	0.3 (0.0–0.6)	0	0.0 (0.0–0.6)	1	0.1 (0.0–0.4)	3	0.1 (0.0–0.2)
Coumarin 5%	1	0.1 (0.0–0.3)	1	0.2 (0.0–0.6)	1	0.2 (0.0–0.5)	0	0.0 (0.0–0.6)	0	0.0 (0.0–0.6)	3	0.1 (0.0–0.2)
Farnesol 5%	8	0.8 (0.2–1.3)	0	0.0 (0.0–0.5)	1	0.2 (0.0–0.5)	3	0.6 (0.0–1.2)	2	0.4 (0.0–0.9)	14	0.5 (0.2–0.7)
Hexylcinnamal 10%	4	0.4 (0.0–0.8)	0	0.0 (0.0–0.5)	0	0.0 (0.0–0.6)	2	0.4 (0.0–0.8)	1	0.2 (0.0–0.6)	7	0.2 (0.0–0.4)
HICC 5%	26	2.5 (1.5–3.4)	4	0.8 (0.0–1.5)	7	1.3 (0.3–2.2)	7	1.3 (0.3–2.2)	5	1.1 (0.2–1.9)	49	1.6 (1.1–2.0)
Sesquiterpene lactone mix 0.1%	1	0.1 (0.0–0.3)	0	0.0 (0.0–0.5)	1	0.3 (0.0–0.6)	1	0.2 (0.0–0.5)	0	0.0 (0.0–0.6)	3	0.1 (0.0–0.2)
Myroxylon periciene	10	1.0 (0.4–1.6)	1	0.2 (0.0–0.6)	4	0.8 (0.0–1.6)	4	0.7 (0.0–1.5)	4	0.9 (0.1–1.6)	24	0.8 (0.5–1.1)

CI, confidence interval; FM, Fragrance mix; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde. ^aTested in only 2740 subjects. ^bCountry subtotals may not add up to the overall total because of the age-standardization procedure.

Table 5 Clinical relevance: avoidance of scented products due to skin complaints and itchy skin rash lasting > 3 days in the lifetime in subjects with contact allergy to different fragrance allergens

	Crude prevalence		+ Avoidance of scented products due to skin problems in lifetime		+ Itchy skin rash lasting > 3 days in lifetime	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
FM I TRUE Test ^a (high atranol and chloratranol)	50	1.8 (1.3–2.4)	28	1.0 (0.7–1.4)	23	0.8 (0.5–1.2)
FM I Finn Chamber (high atranol and chloratranol)	82	2.6 (2.1–3.2)	53	1.7 (1.3–2.2)	42	1.3 (0.9–1.8)
At least one reaction to single substances of FM I	85	2.7 (2.2–3.4)	57	1.8 (1.4–2.3)	41	1.3 (0.9–1.7)
FM I True Test ^a (high atranol and chloratranol) and a single substance	27	1.0 (0.6–1.4)	16	0.6 (0.3–0.9)	12	0.4 (0.2–0.7)
FM I Finn Chamber and a single substance	46	1.5 (1.0–1.9)	34	1.1 (0.7–1.5)	25	0.8 (0.5–1.1)
FM I TRUE Test ^a (high atranol and chloratranol) or a single substance	92	3.4 (2.7–4.0)	56	2.0 (1.5–2.6)	42	1.5 (1.1–2.0)
FM I Finn Chamber or a single substance	105	3.4 (2.7–4.0)	69	2.2 (1.7–2.7)	50	1.6 (1.2–2.1)
FM II Finn Chamber	60	1.9 (1.4–2.5)	41	1.3 (0.9–1.7)	29	0.9 (0.6–1.3)
At least one reaction to single substances of FM II	72	2.3 (1.8–2.8)	52	1.7 (1.2–2.2)	41	1.3 (0.9–1.7)
FM II Finn Chamber and a single substance	50	1.6 (1.2–2.0)	38	1.2 (0.8–1.6)	27	0.9 (0.5–1.2)
FM II Finn Chamber	82	2.6 (2.1–3.2)	55	1.8 (1.3–2.2)	43	1.4 (1.0–1.9)
'Conservative' approach (FM I TRUE Test ^a or FM II or HICC or sesquiterpene lactone mix or <i>Myroxylon pereirae</i>)	113	4.1 (3.4–4.9)	72	2.6 (2.0–3.2)	53	1.9 (1.5–2.5)
'Clinical approach' (FM I TRUE Test ^a or FM II and a single substance, or HICC or sesquiterpene lactone mix or <i>Myroxylon pereirae</i>)	58	2.1 (1.6–2.7)	44	1.6 (1.1–2.1)	33	1.2 (0.8–1.6)

CI, confidence interval; FM, Fragrance mix; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde. ^aTested in only 2740 subjects.

(allergic and/or irritant) instead of the lifetime prevalence of any itchy skin rashes, the prevalence is 0.5% (95% CI 0.3–0.7) (15 of 58 subjects).

Discussion

In this large study, 12 377 subjects participated, and a random sample of 3119 subjects was patch tested. As demonstrated in Table 1, there is no substantial difference in the reported avoidance of scented products of the subjects patch tested compared with the interviewed subjects in six European regions. As demonstrated by Naldi *et al.*,³ the age and sex distribution is consistent with the general population data obtained from Eurostat 2010. There was also no substantial difference in the prevalence of subjects who reported different skin complaints between the patch-tested and the interviewed subjects, and the study employed the highest methodological quality.^{2,4,5}

The prevalence was higher when testing FM I in petrolatum with a high content of atranol and chloratranol (in *E. prunastri*) in Finn Chambers than with FM I in the TRUE Test with the same concentration of *E. prunastri* (Table 2). It is known that the fragrance mix in the TRUE Test is less sensitive to detect fragrance contact allergy than patch testing petrolatum-based test material in Finn Chambers or Van der Bend chambers.⁸ In that retrospective study, of 464 patients positive to FM I Trolab, only 187 (40%) were also positive to FM I TRUE Test, and out of 218 patients positive to FM I TRUE Test, 187 (86%) also reacted to FM I Trolab.⁸ In our study the corresponding figures were 50% and 74%, respectively. In the study of Mortz and Andersen,⁸ only 58% of

patients with a ++ reaction and 86% with a +++ reaction to FM I Trolab had a concomitant reaction to FM I TRUE Test. Theirs was a retrospective study and not all patients were also patch tested with the single ingredients of FM I. Of those 171 patients positive to FM I TRUE Test and also patch tested with the ingredients of FM I, 117 (68.4%) also had a positive reaction to at least one of the single ingredients, and out of those 348 patients positive to FM I Trolab and also patch tested with the ingredients of FM I, 189 (54%) also had a positive reaction to at least one of the single ingredients. There was a strong relationship between the strength of the reaction to the two FM I formulations and the number of positive reactions to the ingredients of FM I. Our findings were very similar (Table 3).

In a systematic review of the literature, Thyssen *et al.*¹ investigated contact allergy to fragrances in the general population. Nineteen studies were identified, of which 13 were performed among adults. Sample sizes varied between 82 and 2545 tested subjects, and 11 648 subjects were tested in total. The weighted average prevalences of FM I and MP sensitization were 3.7% and 1.6%, respectively. The corresponding median prevalences were lower (FM I, 2.3% and MP, 1.1%), probably owing to the small number of included studies. Thyssen *et al.*¹ could not find a study that investigated the prevalence of FM II sensitization in the general population.

Among 12–16 year olds, the prevalences of FM I and MP sensitization were 1.8% and 0.6%, respectively, based on a large study from Odense, Denmark.⁹ The authors repeated the study 15 years later and managed to contact 1206 young adults from the same cohort. The questionnaire was answered

by 899 (74.5%); however, only 442 (36.7%) of those invited participated in patch testing. Most nickel reactions were persistent, and a significant number of new nickel sensitizations were found, but FM I reactions from adolescence could not be reproduced.¹⁰

The prevalence of contact allergy to FM II in the general population has not been reported before. In our study, contact allergy to FM II was diagnosed in 1.9% (95% CI 1.5–2.4), with a higher prevalence in women than in men. Of the constituents of FM II, HICC had the highest prevalence with 1.5% (95% CI 1.1–1.9).

The main strength of the study is that it is population based, and it is rather evident that data from clinical populations will show higher prevalence.^{11–16} In this epidemiological study, we also tried to assess the clinical relevance of positive patch test reactions. In a clinical setting, the diagnosis of allergic contact dermatitis is a three-step procedure. After establishing a diagnosis of contact allergy (immunologically acquired delayed hypersensitivity) it is necessary to demonstrate present exposure to the sensitizer or possibly cross-reacting substances, and then to assess the clinical relevance. This means that the demonstrated exposure should explain/contribute to the dermatitis under investigation with regard to the exposure, localization, type and course of the dermatitis on the one hand, and the degree of reactivity on the other.¹⁷ Thus, the patch test measures only whether an individual is sensitized or not, and a positive patch test reaction is not necessarily an indicator of allergic contact dermatitis, the clinical disease.

Knowledge on the prevalence of contact allergy is important. Allergic contact dermatitis includes knowledge on past and present biological significance, and also the likelihood for the contact allergy to manifest as a clinical disease in the future. As mentioned, a diagnosis of allergic contact dermatitis is the result of a complicated process that is easily influenced by factors such as the knowledge and experience of the dermatologist within the area of contact dermatitis, and also the possibility to perform exposure investigations and to follow the course of the dermatitis over extended periods. It would be enormously advantageous if reliable estimates of exposure, and information on the likely clinical relevance of this exposure could be obtained from questionnaires to which patch-tested individuals have responded, before anything is known about the patch test result. Such an approach has been tried in this epidemiological study, with a number of participants patch tested. The algorithm used requires the presence of contact allergy provided by the patch test, while the questionnaire provides knowledge on the two other factors in the diagnosis of allergic contact dermatitis – exposure and clinical relevance – by requiring avoidance of exposure to the contact sensitizer and a dermatitis lasting > 3 days during the lifetime.

In the general population, the prevalence of fragrance allergy to FM I plus a positive patch test to a single component of FM I was 1.0%, with a clinical relevance of 0.4% according to our algorithm when using the TRUE Test containing *E. prunastri* with a high content of atranol and chloratranol (Table 5). When using the FM I in Finn Chamber

technique, the corresponding prevalences were 1.5% and 0.8%, respectively. The prevalences of a positive patch test to FM II plus a positive patch test reaction to a single component of FM II were 1.6% and 0.9%, respectively, when clinical relevance was considered according to the used algorithm.

We are aware that the algorithm used needs to be validated, and it cannot be used as an instrument to diagnose allergic contact dermatitis in patch-tested populations. To confirm our results on 'relevance' based on patch test data and an epidemiological approach, the gold standard to establish clinical relevance would be to apply a use test such as the repeated open application test in groups with and without contact allergy combined with a positive or negative algorithm.¹⁸ The framework we developed in this study – including the reproducible questionnaire, the study and training documentation, the patch test courses on application and reading, the video on patch test procedures and the definition of clinical relevance – provide useful tools for standardizing methodology in this multicentre and international study. It may be used for future investigations on contact allergies and dermatitis in the general population.

References

- 1 Thyssen JP, Menné T, Linneberg A, Johansen JD. Contact sensitization to fragrances in the general population: a Koch's approach may reveal the burden of disease. *Br J Dermatol* 2009; **160**:729–35.
- 2 Diepgen T, Ofenloch RF, Bruze M *et al.* Prevalence of contact allergy in the general population in different European regions. *Br J Dermatol* 2015; doi: 10.1111/bjd.14167.
- 3 Naldi L, Cazzaniga S, Gonçalo M *et al.* Prevalence of self-reported skin complaints and avoidance of common daily life consumer products in selected European regions. *JAMA Dermatol* 2014; **150**:154–63.
- 4 Rossi M, Coenraads P-J, Diepgen T *et al.* Design and feasibility of an international study assessing the prevalence of contact allergy to fragrances in the general population: the European Dermato-Epidemiology Network Fragrance Study. *Dermatology* 2010; **221**:267–75.
- 5 Bruze M. Thoughts on how to improve the quality of multicentre patch test studies. *Contact Dermatitis* 2015; in press.
- 6 Wilkinson DS, Fregert S, Magnusson B *et al.* Terminology of contact dermatitis. *Acta Derm Venereol* 1970; **50**:287–92.
- 7 Ahmad OB, Boschi-Pinto C, Lopez AD *et al.* Age standardization of rates: a new WHO standard. Available at: <http://www.who.int/healthinfo/paper31.pdf> (last accessed 2 September 2015).
- 8 Mortz CG, Andersen KE. Fragrance mix I patch test reactions in 5006 consecutive dermatitis patients tested simultaneously with TRUE Test® and Trolab® test material. *Contact Dermatitis* 2010; **63**:248–53.
- 9 Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Contact allergy and allergic contact dermatitis in adolescents: prevalence measures and associations. *Acta Derm Venereol* 2002; **82**:352–8.
- 10 Mortz CG, Bindslev-Jensen C, Andersen KE. Prevalence, incidence rates and persistence of contact allergy and allergic contact dermatitis in The Odense Adolescence Cohort Study: a 15-year follow-up. *Br J Dermatol* 2013; **168**:318–25.
- 11 Nardelli A, Carbonez A, Drieghe J, Goossens A. Results of patch testing with fragrance mix 1, fragrance mix 2, and their ingredients, and *Myroxylon pereirae* and colophonium, over a 21-year period. *Contact Dermatitis* 2013; **68**:307–13.

- 12 Krautheim A, Uter W, Frosch P *et al.* Patch testing with fragrance mix II: results of the IVDK 2005–2008. *Contact Dermatitis* 2010; **63**:262–9.
- 13 Fransway AF, Zug KA, Belsito DV *et al.* North American contact dermatitis group patch test results for 2007–2008. *Dermatitis* 2013; **24**:10–21.
- 14 Mann J, McFadden JP, White JML *et al.* Baseline series fragrance markers fail to predict contact allergy. *Contact Dermatitis* 2014; **70**:276–81.
- 15 Heisterberg MV, Menné T, Johansen JD. Contact allergy to the 26 specific fragrance ingredients to be declared on cosmetic products in accordance with the EU cosmetics directive. *Contact Dermatitis* 2011; **65**:266–75.
- 16 Frosch PJ, Duus Johansen J, Schuttelaar MLA *et al.* Patch test results with fragrance markers of the baseline series – analysis of the European Surveillance System on Contact Allergies (ESSCA) network 2009–2012. *Contact Dermatitis* 2015; **73**:163–71.
- 17 Bruze M. What is a relevant contact allergy? *Contact Dermatitis* 1990; **23**:224–5.
- 18 Nakada T, Hostynek JJ, Maibach HI. Use tests: ROAT (repeated open application test)/PUT (provocative use test): an overview. *Contact Dermatitis* 2000; **43**:1–3.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1. Details of the patch tests.