

ESSCA results with the baseline series, 2002–2012: *p*-phenylenediamine

Marie-Louise A. Schuttelaar¹, Tatiana A. Vogel¹, Francesca Rui², Beata Kręcis^{3,4}, Dorota Chomiczewska-Skora⁴, Marta Kieć-Świerczyńska⁴, Wolfgang Uter⁵ and Francesca Larese Filon²

¹Dermatology, University Medical Center Groningen, University of Groningen, 9700 RB, Groningen, The Netherlands, ²Department of Medical Sciences, Clinical Unit of Occupational Medicine, University of Trieste, 34129, Trieste, Italy, ³Faculty of Health Science, Jan Kochanowski University, 25-317, Kielce, Poland, ⁴Department of Dermatology, Nofer Institute of Occupational Medicine, 90-950, Lodz, Poland, and ⁵Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen/Nürnberg, 91054, Erlangen, Germany

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Summary

Background. Allergic contact dermatitis caused by *p*-phenylenediamine (PPD) is common among all age groups and both sexes. Monitoring of prevalence and intensity of sensitization is important.

Objective. To evaluate contact allergy to PPD in Europe, and to compare reaction intensities in different European regions.

Methods. Data collected by the European Surveillance System on Contact Allergies (ESSCA) network between 2002 and 2012 from 12 European countries were analysed regarding prevalence, grading of positive reactions to PPD, and relevance.

Results. A total of 99 926 PPD-positive patients from 63 departments were included for analysis. The overall (2002–2012) prevalence of PPD sensitization in Europe is ~4%. Stratified for country, the highest overall standardized prevalence was found in Lithuania, and the lowest in Slovenia. The prevalence of PPD sensitization did not decline over the years. In the southern European countries, higher numbers of strong and extremely strong reactions were registered. The clinical relevance of PPD sensitization varied from half to three-quarters.

Conclusion. The prevalence of PPD sensitization has not changed over time. Strong and extremely strong patch test reactions are seen more often in the South, probably because of the higher number of PPD-containing hair dye products.

Key words: allergic contact dermatitis; CAS no. 106-50-3; contact allergy; European baseline series; *p*-phenylenediamine; patch tests.

Correspondence: Marie-Louise Anna Schuttelaar, Department of Dermatology, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands. Tel: + 31 50 361 2520; Fax: +31 50 361 2624. E-mail: m.l.a.schuttelaar@umcg.nl

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The aromatic amine *p*-phenylenediamine (PPD) (1,4-diaminobenzene, CAS no. 106-50-3) is a chemical that acts as an intermediate in dyes and antioxidants. PPD is the most well-known ingredient of oxidative (permanent) hair dye products, and the only one that is regularly patch tested in the (European) baseline series. Its extreme protein-binding capacity and its low molecular weight enable PPD to easily penetrate the hair shaft, but also make it a potent sensitizer that is able to cause severe contact allergic reactions (1). Most cases of contact allergy to PPD occur in consumers and hairdressers after contact with hair dye products.

For several decades, PPD has been tested in the European baseline series. The prevalence of contact allergy to PPD in consecutive eczema patients varies widely between the different countries in Europe (2). Thyssen et al. reported a weighted prevalence average of 4% in Europe (3).

The objective of this study was to evaluate contact allergy to PPD in patients with suspected allergic contact dermatitis who were patch tested at departments of the European Surveillance System on Contact Allergies (ESSCA) network in the period from 2002 to 2012. Furthermore, in this study we compared the frequency of contact allergy to PPD and the reaction strength during patch testing between two different regions of Europe: North/Central and South.

Methods

The analyses in the present study are based on data included in the database of the network of the ESSCA (www.essca-dc.org). This network has been described previously (2). Patch test results were obtained with the European baseline series, with possible national or departmental adaptations. These results were included in the database along with clinical and demographic data. The detailed characteristics of patients of the most recent period of analysis (2009–2012) have been published (4). The present article addresses the frequency and time course (2002–2012) of sensitization to PPD in consecutive patients who were patch tested in 12 European countries. These European countries include Austria, Switzerland, Germany, Denmark, Spain, Finland, Italy, Lithuania, The Netherlands, Poland, Slovenia, and the United Kingdom.

In Austria, PPD 1% pet. has not been tested routinely since 2008, and in Germany it has not been tested since 2005, except in special cases, for example evaluation of occupational contact allergy in hairdressers. This makes interpretation of these data difficult, and they have therefore been omitted from the analysis. Slovenia has participated in the ESSCA network since 2009, so data on PPD allergy have been available only since that time.

The countries are classified into two regions to identify regional differences. These regions were defined as follows: North/Central – Finland, Denmark, Lithuania, Poland, Germany, Austria, Switzerland, The Netherlands, and the United Kingdom; and South – Spain, Italy, and Slovenia.

All patients included in the present analysis were patch tested with either PPD 1% pet. in investigator-loaded systems or in the TRUE Test® (at a concentration of 0.090 mg/cm²). The vast majority of patch tests were

investigator-loaded; 5145 of the consecutive patients were patch tested with the TRUE Test®, in five departments altogether. Most of these patients were tested with the TRUE Test® in The University Medical Centre Groningen (The Netherlands; n = 3987), followed by Hospital Universitario de La Princesa Madrid (Spain; n = 718), the Department of Dermatology at León hospital (Spain; n = 242), the Amsterdam Free University Medical Centre (The Netherlands; n = 180), and the Murcia department (Spain; n = 18).

The patch testing procedure was conducted according to international recommendations, and readings were performed according to the European Society of Contact Dermatitis criteria (5). The reading of patch test reactions was based on inspection and palpation of the morphology (erythema, infiltrate, papules, and vesicles). The symbols of the patch test reactions are as follows: –, no reaction; +/?, doubtful; +, weak positive; ++, strong positive; +++, extremely positive; IR, irritant reaction.

At least one reading was performed between day (D) 3 and D5 (inclusive) after application of the patch test. Weak, strong and extremely strong positive patch test reactions were considered to be positive. From 2007 onwards, aggregated data were exported from Copenhagen/Gentofte (Denmark). The Slovenian departments contributed dichotomized information on reactions being positive or non-positive. Hence, the distribution of reaction grades cannot be examined for these data.

Relevance was based on patient interviews, and was assessed by the physicians consulted. A clinically relevant patch test reaction was defined as follows: positive patch test reactions (+/++/+++) to PPD in a subject with a current or a past dermatitis reaction, certainly or probably caused or aggravated by exposure to a source of PPD. Analysis of clinical relevance of positive reactions was restricted to (i) departments patch testing with PPD and (ii) departments documenting relevance. The proportion of relevant reactions was based on non-missing data; that is, missing data were considered to be completely missing at random. In other words, the patients with information were considered to be representative for all patients. All individuals with PPD contact allergy in whom the occupational code 5141 (ISCO-88) was documented were identified. Although this code also includes beauticians, experience indicates that >90% of these individuals are hairdressers. The proportion of relevance restricted to this group of hairdressers and the proportion of occupationally relevant positive PPD reactions were analysed separately.

Data management and analysis were performed with the statistical software R (version 3.1.3; www.r-project.org). In particular, besides crude

prevalences of PPD contact allergy stratified for country and age, age- and sex-standardized prevalences with accompanying 95% confidence intervals (CIs) were also calculated. This allows the analysis of a comparison which is unconfounded concerning these two variables.

Results

The prevalence of PPD sensitization in the European countries

A total of 100 191 consultations involved patch testing with the European baseline series with PPD 1% pet. or in the TRUE Test®. Owing to re-consultation of some patients, for whom the most current consultation was chosen, a total of 99 926 patients were included for further analysis. Overall, the United Kingdom had tested the largest number of individuals each year. Spain, The Netherlands and Poland showed an increase in the number of patients who were patch tested with the baseline series, and thus PPD, from, respectively 2009, 2009 and 2011 onwards.

The prevalence of sensitization to PPD stratified for the 12 European countries is shown in Table S1. Differences in the prevalence rates of sensitization are marked by year. Overall, the prevalence of PPD sensitization varied around 4%, and seemed to be stable over the included years. There was no remarkable difference between crude and age-standardized and sex-standardized prevalence rates. The highest prevalence of 9.3% in consecutive patients was seen in 2006 in Lithuania, which had joined the ESSCA in 2004. The prevalence in the Lithuanian department was also relatively high in later years. The lowest prevalences were found in Italy in 2002 (0.7%), albeit on the basis of quite limited data ($n = 185$ tested), followed by Denmark in 2003 (1.5%).

Table 1 shows data on the overall (2002–2012 combined) prevalences of PPD sensitization stratified for country. Among all included countries, Lithuania showed the highest overall standardized prevalence of PPD sensitization, at 5.8%, followed by Austria (5.3%). The lowest prevalences were found in Slovenia (2.3%) and Denmark (2.5%). The prevalence of sensitization to PPD stratified for the 12 European countries, year and sex is shown in Table S2. In general, more women than men were patch tested. Approximately three-quarters of all positive reactions to PPD were seen in women, varying from 65% in Germany to almost 87% in Slovenia. The highest prevalence among women was seen in Austria (6.1%), and the highest prevalence among men was seen in Lithuania (7.0%). The lowest prevalences were seen in Denmark and Slovenia. Only in Lithuania was the prevalence of

PPD sensitization among men (7.0%) higher than that among women (5.1%), although not significantly, considering the overlapping 95% CIs.

The grades of patch test results for all patients who reacted positively to PPD, marked by country, are also shown in Table 1. Strong and extremely strong patch test reactions are combined as one group. In general, in most of the countries, more strong/extremely strong positive reactions than weak positive reactions were observed. Only in Austria, Germany, Lithuania and The Netherlands were more weak positive than strong/extremely strong positive reactions seen.

In Table 2, the number of individuals with a positive patch test reaction per country, combined with the percentage of clinically relevant reactions, is shown. Of the 63 departments participating in the ESSCA network, a total of 49 departments routinely documented clinical relevance. This indicates that 50–75% of all PPD-positive patch test reactions were considered to be clinically relevant. The number of PPD-sensitized hairdressers and the percentage of relevant PPD sensitizations among hairdressers are shown, the latter being between 66% and 100%. Overall, however, occupationally relevant reactions were uncommon, varying from 0.5% to nearly 20% (in the United Kingdom and Poland, respectively).

Differences in the prevalence and patch test strength of PPD sensitization between two European regions

Figure 1 shows the annual age- and sex-standardized prevalence rates of sensitization to PPD stratified for two European regions. The Northern/Central region and the South showed similar prevalences at ~4%. Within the European regions, some variability was noted, but no definite trend.

The distribution of the strength of the positive patch test reactions was compared between the two regions in Europe. The results are shown in Fig. 2, in which strong positive (++) and extremely positive (+++) reactions are combined. These were significantly more frequent in the South ($p < 0.001$, χ^2 -test). Slovenia was excluded in this analysis, as only a dichotomous outcome was available.

Discussion

Prevalence of PPD sensitization

This study shows the development of sensitization to PPD from 2002 to 2012, in 12 European countries and stratified in two regions. The overall prevalence of ~4% was largely stable during the study period. The maximum permitted concentration of PPD in consumer products was

Table 1. Results obtained with *p*-phenylenediamine (1% pet. or included in the TRUE Test®) in dermatitis patients in the European Surveillance System on Contact Allergies network, 2002–2012, stratified for country

Country	n (test)	+, n (%)	++/+++, n (%)	?/IR, n (%)	Males	Females	Overall	Standardized
					Positive, n (%) 95%CI	Positive, n (%) 95%CI	Positive, n (%) 95%CI	Positive (%) 95%CI
Austria	1 807	56 (3.1)	37 (2)	0 (0)	17 (3.1) 1.8–4.9	76 (6.1) 4.8–7.5	93 (5.1) 4.2–6.3	5.3 4.2–6.3
Switzerland	4 969	90 (1.8)	123 (2.5)	147 (3)	55 (2.9) 2.2–3.7	158 (5.2) 4.4–6	213 (4.3) 3.7–4.9	4.4 3.8–5
Germany	5 485	111 (2)	99 (1.8)	65 (1.2)	72 (3.4) 2.6–4.2	138 (4.1) 3.5–4.9	210 (3.8) 3.3–4.4	3.8 3.3–4.4
Denmark ^a	6 315	– (0.9)	– (1.2)	– (3.6)	46 (2.2) 1.6–3.0	109 (2.6) 2.1–3.1	155 (2.5) 2.1–2.9	2.5 2.1–2.9
Spain	5 582	26 (0.5)	213 (3.8)	2 (0)	57 (3.2) 2.4–4.1	182 (4.8) 4.1–5.5	239 (4.3) 3.8–4.8	4 3.5–4.5
Finland	2 913	39 (1.3)	75 (2.6)	43 (1.5)	29 (2.8) 1.9–4.0	85 (4.6) 3.7–5.6	114 (3.9) 3.2–4.7	3.9 3.2–4.6
Italy	19 483	221 (1.1)	432 (2.2)	71 (0.4)	136 (2.0) 1.7–2.3	517 (4.1) 3.8–4.5	653 (3.4) 3.1–3.6	3.4 3.1–3.6
Lithuania	1 823	64 (3.5)	37 (2)	9 (0.5)	28 (7.0) 4.7–9.9	73 (5.1) 4.0–6.4	101 (5.5) 4.5–6.7	5.8 4.6–7.0
The Netherlands	8 604	183 (2.1)	129 (1.5)	61 (0.7)	79 (2.6) 2.0–3.2	233 (4.2) 3.7–4.8	312 (3.6) 3.2–4.0	3.6 3.2–4.0
Poland	4 588	55 (1.2)	160 (3.5)	8 (0.2)	49 (3.6) 2.7–4.7	166 (5.1) 4.4–6.0	215 (4.7) 4.1–5.3	4.6 4.0–5.3
Slovenia ^b	5 224	– (–)	– (–)	– (–)	16 (1.0) 0.6–1.6	106 (2.9) 2.4–3.5	122 (2.3) 1.9–2.8	2.3 1.9–2.8
United Kingdom	33 133	541 (1.6)	788 (2.4)	108 (0.3)	267 (2.5) 2.2–2.8	1062 (4.8) 4.5–5.0	1329 (4.0) 3.8–4.2	3.9 3.7–4.1
Overall ^c	99 926	– (1.5)	– (2.3)	– (0.8)	851 (2.5) 2.4–2.7	2905 (4.4) 4.2–4.5	3756 (3.8) 3.6–3.9	3.7 3.6–3.9

IR, irritant reaction; ?, doubtful reaction; '–', not calculable. CI, confidence interval.

^aFor 2007–2011, only dichotomized reaction available; proportions based on previous data.

^bOnly dichotomized reaction available.

^cPartly only dichotomized reaction available; hence, no absolute numbers; proportions based on available data.

limited to 2% in the final product in 2009 [amending Annex III to Regulation (EC) No. 1223/2009 of the European Parliament and of the Council on cosmetic products]. The Cosmetics Regulation put into force in 2009 became effective immediately, in contrast to the previous (amendments of the) Cosmetics Directive, which had to be translated into national law. However, the time period after the regulation is too short to expect a decrease in PPD sensitization in the current study. Moreover, it is not known whether, or to what extent, the concentration of PPD in hair dye products has actually been reduced following the reduction in the maximum permitted concentration. Other sources of PPD exposure that are not covered by the regulation are temporary black henna tattoos, which can contain high concentrations of PPD (6). A study performed in Denmark showed that a 19.0% of hairdressers and 6.3% of participants from the general population had ever had a temporary black tattoo (7). More recently, a population-based study in the general

population of five European countries reported that 5.5% of the subjects had had a temporary black henna tattoo. A strong and significant association was observed between black henna tattoo use and PPD contact allergy (8). The countries that contributed less, as defined according to the number of individuals patch tested over the total time period, showed wider variation in prevalence, which is indicative of chance variation.

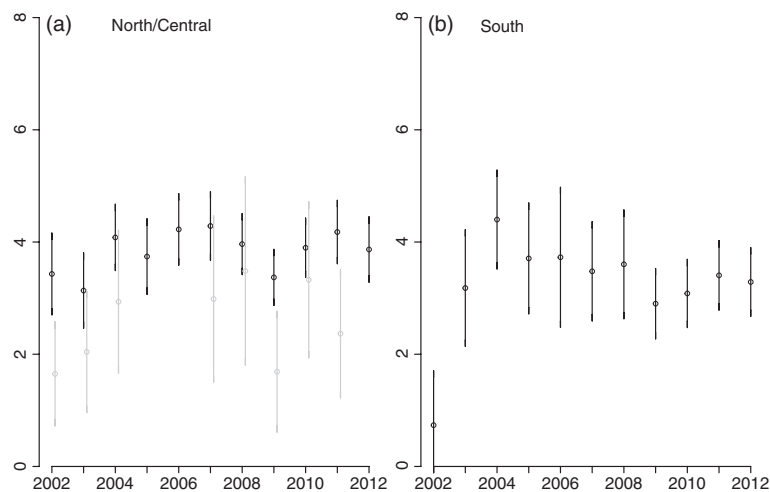
The other main observation concerning spatiotemporal variation is the variation of the overall (2002–2012) prevalence of sensitization to PPD between countries, namely, from 2.5% in Denmark to 5.8% in Lithuania. These differences in prevalence between countries are not straightforward to explain, for example, by demographic characteristics, as these should be fairly similar. Neither can they be explained by the number of tested individuals, although the number of contributing hospitals per country may have some impact, in the sense that, if just one department provides data, it may be an 'outlier' in its

Table 2. Relevance of positive reactions to *p*-phenylenediamine (PPD) (1% pet. or included in the TRUE Test®) obtained in dermatitis patients in the European Surveillance System on Contact Allergies network, 2002–2012, stratified for country

Country	n (positive)	% (relevant)	n (hairdressers positive/tested)	% (hairdressers relevant)	% (occupationally relevant)
Austria	93	56.7	9/65	66.7	3.3
Switzerland	213	41.6	14/90	78.6	4.8
Germany	210	46.6	4/54	75	3.1
Spain	239	20.9	19/106	75	11.6
Finland	114	18.2	7/98	0	1.5
Italy	653	72.2	113/424	72.1	11.6
Lithuania	101	77.8	6/18	100	6.7
The Netherlands	312	63.9	27/237	87.5	8.4
Poland	215	62.6	26/132	96	18.5
United Kingdom	1329	77.5	66/385	98.3	0.5

Current and past relevance, certain or probable or not qualified regarding certainty, have been aggregated. Denmark and Slovenia are excluded, as relevance information was not available (for a large part of the data). Analysis of relevance of positive reactions was restricted to (i) departments testing with PPD and (ii) departments documenting relevance at all ($n = 49$).

The second and fourth columns, respectively, show the number of positive reactions overall (see also Table 1) and the number of hairdressers with positive reactions to PPD. It should be noted that 'hairdressers' include a small proportion of beauticians, as these have been coded together in the ISCO-88 classification. '% (relevant)': overall, i.e. irrespective of currentness and occupation. '% (hairdressers relevant)': proportion of relevance restricted to hairdressers. '% (occupational relevant)': the proportion of occupationally relevant positive PPD reactions irrespective of a certain occupation or the presence of occupational dermatitis.

**Fig. 1.** Age- and sex-standardized annual prevalences in the two European regions, a. North/Central and b. South 2002–2012, with accompanying 95% confidence intervals. The Danish figures are indicated separately as grey symbols in the 'North/Central' region.

own country (4). Possibly, trends in fashion or changes in occupational exposure are the cause of this difference. Furthermore, other factors, such as patterns of referral of patients to patch test clinics, could contribute to variations in patch test results between departments and countries (4). For example, the low prevalence in Denmark could be explained by the relatively easy access to dermatological care in Denmark.

In all, both the percentage of PPD-sensitized females and the general prevalence of PPD sensitization are highly comparable with those found in previous studies (3). In accordance with our results, Thyssen et al. also reported that more women (3.9%) than men (3.6%) were sensitized in Europe. This corresponds to higher exposure among women (3). A European cross-sectional study in

the general population reported that 50.9% of individuals had used hair colorants at least once in their lifetime; 78% of them were female and 20% were male (8). A Danish study in the adult general population reported similar results; 74% of the female respondents and 18% of the male respondents dyed their hair at least once in their lifetime (9). The differing results in Lithuania should probably not be overinterpreted, as the sex difference is not significant.

The use of PPD derivatives has increased considerably; a market survey performed in Germany, for instance, showed that PPD itself is currently found in only 0.3% of oxidative hair dye products (10). This study, performed in 2013–2014, showed that toluene-2,5-diamine (TDA) (CAS no. 95-70-5; syn. *p*-toluenediamine) was used

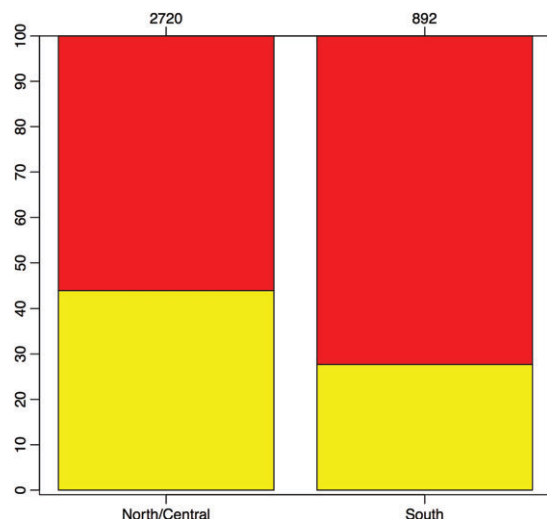


Fig. 2. Proportions of + (yellow) and ++ or +++ (red) reactions among all positive reactions as percentages in two regions: 'South', comprising Spain and Italy; and 'North/Central', comprising the remainder (Slovenia has been excluded in this analysis, as only a dichotomous outcome was available). Total numbers of positive reactions are given at the top.

much more commonly than PPD. However, it is unknown whether this is the result of a recent change or whether it has been the situation for many years.

Recently, the introduction of a methoxymethyl side chain into PPD resulted in the development of a new hair dye molecule: 2-methoxymethyl-*p*-phenylenediamine (ME-PPD) (CAS no. 337906-36-2). Apart from its hair-colouring property, this PPD derivative has significantly lower skin-sensitizing capacity than PPD and TDA (11). ME-PPD was introduced in 2014 to replace PPD and TDA, but was included in only one hair dye series for professional use. The introduction of this PPD derivative could not have influenced the prevalence rates in the current study.

In Spain, The Netherlands, and Poland, a major increase in the number of patch tested individuals was seen. This can be explained by an increased number of patch tested individuals in general. However, in The Netherlands, this could be attributable to centralization of hospital care, with specialized functions of the hospitals. Therefore, more patients were patch tested in the specialized centres, which also contribute to the ESSCA network. In Germany, most, if not all, Information Network of Departments of Dermatology (IVDK) departments had ceased to test with 1% PPD pet. in 2005, owing to safety concerns. This could result in a selection bias of tests recorded thereafter, as patients in whom PPD contact allergy is strongly suspected are more likely to be tested. Hence, the German results from 2005

onwards, and the Austrian results from 2008 onwards, were excluded.

The clinical relevance of the patch test reaction is often difficult to determine. When exposure to PPD occurred in the past, and there is no history of exposure to hair dyes or a black henna tattoo with subsequent skin complaints, the source is often unclear and unreliable. Nevertheless, in the current study, approximately half to three-quarters PPD patch test reactions were clinically relevant, irrespective of occupation, and summarizing previous and current relevance. The proportion of positive reactions to PPD with occupational relevance was much lower, which is not surprising, because occupational exposure occurs mainly in hairdressers, and the number of hairdressers with PPD contact allergy was low (291 of 1639 tested; Table 2). In hairdressers, sensitization was very often considered to be relevant, although, in some countries, positive reactions were regarded as relevant in only three-quarters of the hairdressers. However, we assume that PPD is normally relevant for hairdressers, at least in terms of elicitation, for example if cutting hair after dyeing. Possibly, evaluating dermatologists were unaware of cross-reacting occupational material even if PPD was avoided in hairdressers, or considered protection to be perfect if gloves were worn during hair dyeing. Of course, induction may have taken place though hairdressers dyeing their own hair (12, 13).

In 2008, Schnuch et al. also investigated sources of exposure in PPD-positive patients diagnosed by the IVDK. They followed an algorithm with selection criteria according to assumed causal exposure and other criteria such as the affected anatomical site, namely, face or hand (14). In this study 21.5% of positive PPD patch test reactions were attributed to consumer-exposure to hair dye products. However, these data are difficult to compare with our data with regard to relevance. Additional patch testing with the hairdressers series or testing with suspected cosmetics was a criterion for 'profiling' in their study, for instance, whereas in our study we solely relied on PPD data obtained with the baseline series. Of the PPD-positive patients, 35% were allocated to the 'occupational exposure' group in their study, whereas our data show lower percentages, varying from 0.5% to 18.5%. The higher percentage in the German study can be explained by the fact that both occupational cause and hand eczema were used to define the 'occupational exposure' group.

Differences in sensitization prevalence and reaction intensity of PPD patch tests between two regions in Europe

Thyssen et al. reported that PPD sensitization was more prevalent in central and southern European patch test

centres than in the Scandinavian departments (3, 15). These results are difficult to compare with our results, owing to a different composition of the regions (see below). In the current study, we could not show a higher prevalence of PPD contact allergy in the South than in the North/Central region. This may further be explained by differences in the included countries and patch test departments. One could suggest other groupings of the contributing countries, as socioeconomic status and ethnic groups vary widely between the countries. This makes the grouping of countries somewhat arbitrary. In the northern region, Thyssen et al. included two departments from Denmark and one department from Sweden. These departments had overall low PPD positivity prevalence rates: 2.8% and 2.9% for Denmark, and 2.1% for Sweden. In the current study, the North/Central region departments include, among others, one department in Denmark, with an overall prevalence of PPD sensitization of 2.5%. Although the prevalence of PPD sensitization in Denmark is comparable to the study of Thyssen et al., and, in fact, the data overlap with those of that study, the prevalences of the other included countries are far higher.

The reasons for the differences in the strength of the PPD patch test reaction between countries are partly a matter of speculation. One explanation could be differences in natural hair colour. Individuals in southern Europe have, predominantly, darker hair than those in, for example, Denmark and Sweden, who mostly have natural blonde hair. We assume that people who have naturally blonde hair will more often dye their hair blonde when it turns grey than will individuals with dark hair, who will probably use darker shades. It is known that dark hair dyes contain higher concentrations of PPD, which means that consumers are exposed to higher concentrations of PPD. Hence, they are more at risk of PPD sensitization (16, 17). However, this applies only for hair dye products containing PPD, and not for those containing TDA, which often is used instead of PPD. The degree of sensitization can be shown quite well by the strength of the patch test reaction at elicitation, that is, whether the reaction is +, ++, or +++, or possibly a positive reaction being seen to PPD diluted by ≥ 2 orders of magnitude (18). We showed a higher number of strong positive and extremely positive patch test reactions to PPD in the South than in the North/Central region. The strength of the elicitation reaction to PPD can be influenced by the dose/area of PPD at induction. Hair dyeing with predominantly dark colours, and thus exposure to higher PPD concentrations, could account for the higher number of strong positive and extremely positive patch test reactions in southern Europe.

Market surveys on the active components of oxidative hair dyes have been conducted in several European countries; one survey was performed in the United States. Yazar et al. performed a market survey in Sweden, and showed that 16% of the hair dye products contained PPD according to the labels, whereas 80% contained TDA (19). A market survey in Denmark showed that 22.2% of the investigated hair dyes contained PPD, whereas 58% contained TDA (20). In Germany, only 0.3% of the oxidative hair dyes contained PPD, and TDA was the most commonly used hair dye ingredient, appearing in 88% of the hair dye products (10). In Spain, PPD (50%) is used as often as TDA (49%) in hair dyes (21). In the United States, much more PPD (78%) than TDA (21%) is used in hair dyes (22).

The Spanish survey, which showed that 50% of the hair dyes contained PPD, indicates higher exposure to PPD in Spain among individuals who dye their hair than in other European countries, where TDA is the major allergen in hair dyes. However, the high exposure to PPD in Spain is not reflected in a higher PPD positivity rate in the current study. Hair dye products for home use possibly contain more strong sensitizers, and perhaps in higher concentrations, to achieve a similar effect as products marketed only to hairdressers (21, 22).

Conclusions

The prevalence of PPD sensitization in referred eczema patients is high but has remained stable over the years; no remarkable decreases in PPD sensitization were observed within the patch test population per country and overall. Overall, more women than men were sensitized. Higher numbers of strong positive and extremely strong patch test reactions were observed in the South than in the North/Central region. Monitoring of prevalence and reaction strength of PPD sensitization remains of great importance, as local, regional and European trends can be noticed and regulations can be adjusted.

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References

- Basketter D A, Goodwin B F. Investigation of the prohapten concept. Cross reactions between 1,4-substituted benzene derivatives in the guinea pig. *Contact Dermatitis* 1988; **19**: 248–253.
- Uter W, Aberer W, Armario-Hita J C et al. Current patch test results with the European baseline series and extensions to it from the 'European Surveillance System on Contact Allergy' network, 2007–2008. *Contact Dermatitis* 2012; **67**: 9–19.
- Thyssen J P, White J M. European Society of Contact Dermatitis. Epidemiological data on consumer allergy to p-phenylenediamine. *Contact Dermatitis* 2008; **59**: 327–343.
- Uter W, Gefeller O, Giménez-Arnau A et al. Characteristics of patients patch tested in the European Surveillance System on Contact Allergies (ESSCA) network, 2009–2012. *Contact Dermatitis* 2015; **73**: 82–90.
- Johansen J D, Aalto-Korte K, Agner T et al. European Society of Contact Dermatitis guideline for diagnostic patch testing – recommendations on best practice. *Contact Dermatitis* 2015; **73**: 195–221.
- de Groot A C. Side-effects of henna and semi-permanent 'black henna' tattoos: a full review. *Contact Dermatitis* 2013; **69**: 1–25.
- Hansen H S, Johansen J D, Thyssen J P et al. Personal use of hair dyes and temporary black tattoos in Copenhagen hairdressers. *Ann Occup Hyg* 2010; **54**: 453–458.
- Diepgen T L, Naldi L, Bruze M et al. Prevalence of contact allergy to p-phenylenediamine (PPD) in the European general population. *J Invest Dermatol* 2016; **136**: 409–415.
- Sosted H, Hesse U, Menné T et al. Contact dermatitis to hair dyes in a Danish adult population: an interview-based study. *Br J Dermatol* 2005; **153**: 132–135.
- Kirchlecher S, Hübner A, Uter W. Survey of sensitizing constituents of oxidative hair dyes (retail and professional products) in Germany. *J Dtsch Dermatol Ges* (accepted).
- Goebel C, Troutman J, Hennen J et al. Introduction of a methoxymethyl side chain into p-phenylenediamine attenuates its sensitizing potency and reduces the risk of allergy induction. *Toxicol Appl Pharmacol* 2014; **274**: 480–487.
- Antelmi A, Young E, Svedman C et al. Are gloves sufficiently protective when hairdressers are exposed to permanent hair dyes? An in vivo study. *Contact Dermatitis* 2015; **72**: 229–236.
- Lind M L, Boman A, Sollenberg J et al. Occupational dermal exposure to permanent hair dyes among hairdressers. *Ann Occup Hyg* 2005; **49**: 473–480.
- Schnuch A, Lessmann H, Frosch P J, Uter W. para-Phenylenediamine: the profile of an important allergen. Results of the IVDK. *Br J Dermatol* 2008; **159**: 379–386.
- Thyssen J P, Andersen K E, Bruze M et al. p-Phenylenediamine sensitization is more prevalent in central and southern European patch test centres than in Scandinavian: results from a multicentre study. *Contact Dermatitis* 2009; **60**: 314–319.
- Friedmann P S. The relationships between exposure dose and response in induction and elicitation of contact hypersensitivity in humans. *Br J Dermatol* 2007; **157**: 1093–1102.
- Kligman A M. The identification of contact allergens by human assay. 3. The maximization test: a procedure for screening and rating contact sensitizers. *J Invest Dermatol* 1966; **47**: 393–409.
- Thomas B R, White I R, McFadden J P, Banerjee P. Positive relationship – intensity of response to p-phenylenediamine on patch testing and cross-reactions with related allergens. *Contact Dermatitis* 2014; **71**: 98–101.
- Yazar K, Boman A, Lidén C. Potent skin sensitizers in oxidative hair dye products on the Swedish market. *Contact Dermatitis* 2009; **61**: 269–275.
- Poulsen P B, Strandén M. *Survey and Occurrence of PPD, PTD and Other Allergenic Hair Dye Substances in Hair Dyes*. Copenhagen, The Danish Environmental Protection Agency, 2013.
- Yazar K, Boman A, Lidén C. p-Phenylenediamine and other hair dye sensitizers in Spain. *Contact Dermatitis* 2012; **66**: 27–32.
- Hamann D, Hamann C R, Thyssen J P, Lidén C. p-Phenylenediamine and other allergens in hair dye products in the United States: a consumer exposure study. *Contact Dermatitis* 2014; **70**: 213–218.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Results with PPD (1% pet. or included in the TRUE Test®) in dermatitis patients obtained in the European Surveillance System on Contact Allergies network 2002–2012, stratified for country and year. 1: Crude percentage positive (number of positive reactions/number of patients tested). 2: Age-standardized and sex-standardized percentage positive [95% confidence interval (CI)].

Table S2. Results with PPD (1% pet. or included in the TRUE Test®) in dermatitis patients obtained in the European Surveillance System on Contact Allergies network 2002–2012, stratified for country, year, and sex. Crude percentage positive (number of positive reactions/number of patients tested).

Online supplementary Table S1: Results with PPD (1% pet. or included in the TRUE-test®) in dermatitis patients obtained in the European Surveillance System on Contact Allergy network 2002-2012, stratified for country and year. 1: Crude percent positive (number of positive reactions/ number of patients tested). 2: Age- and sex-standardised percent positive [95% confidence interval (CI)].

Country		2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
Austria	1	4.2% (16/378)	2.4% (8/332)	7.4% (25/339)	4.0% (12/297)	7.5% (26/346)	5.2% (6/115)	N.T.	N.T.	N.T.	N.T.	N.T.	5.1% (4.2-6.3)
	2	4.5% (2.3-6.7%)	2.6% (0.8-4.5%)	7.8% (4.8-10.9%)	4.0% (1.7-6.3%)	7.5% (4.6-10.3%)	3.9% (0.9-6.9%)	N.T.	N.T.	N.T.	N.T.	N.T.	5.3% (4.2-6.3)
Switzerland	1	–	–	–	–	2.5% (6/243)	4.8% (42/872)	4.8% (42/866)	3.2% (12/380)	5.2% (47/906)	4.2% (39/921)	3.2% (25/781)	4.3% (3.7-4.9)
	2	–	–	–	–	2.8% (0.5-5%)	4.9% (3.4-6.4%)	4.8% (3.3-6.3%)	4.4% (1.9-6.8%)	5.0% (3.5-6.5%)	4.1% (2.7-5.4%)	3.4% (2-4.9%)	4.4% (3.8-5.0)
Germany	1	5.0% (72/1431)	3.5% (48/1367)	3.9% (49/1248)	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	3.8% (3.3-4.4)
	2	4.7% (3.6-5.9%)	3.5% (2.4-4.5%)	3.9% (2.7-5%)	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	3.8% (3.3-4.4)
Denmark	1	1.9% (17/903)	1.4% (11/795)	3.2% (25/772)	–	–	2.8% (19/671)	3.2% (20/632)	1.7% (13/749)	3.4% (28/830)	2.3% (22/963)	–	2.5% (2.1-2.9)
	2	1.7% (0.8-2.5%)	1.5% (0.6-2.5%)	2.9% (1.8-4.1%)	–	–	3% (1.6-4.4%)	3.5% (1.9-5%)	1.7% (0.7-2.7%)	3.3% (2-4.6%)	2.4% (1.3-3.4%)	–	2.5% (2.1-2.9)
Spain	1	–	–	8.2% (28/340)	7.5% (28/371)	5.4% (10/185)	4.2% (17/400)	5.9% (7/118)	3.0% (36/1213)	3.3% (34/1029)	3.6% (40/1098)	4.7% (39/828)	4.3% (3.8-4.8)
	2	–	–	7.9% (4.9-10.8%)	6.8% (4.2-9.4%)	4.4% (1.7-7.2%)	3% (1.5-4.5%)	4.1% (1.2-7%)	2.6% (1.7-3.4%)	3.2% (2.1-4.3%)	3.5% (2.4-4.6%)	5.1% (3.4-6.7%)	4.0% (3.5-4.5)
Finland	1	–	3.2% (9/281)	2.0% (7/345)	2.5% (6/237)	4.6% (11/240)	5.4% (20/369)	4.9% (19/391)	2.3% (7/302)	3.3% (10/303)	5.4% (17/313)	6.1% (8/132)	3.9% (3.2-4.7)
	2	–	2.7% (0.9-4.5%)	2.2% (0.5-3.8%)	2.2% (0.4-4%)	4.4% (1.8-6.9%)	5.3% (3-7.7%)	4.7% (2.5-6.8%)	2.6% (0.7-4.5%)	3.3% (1.2-5.3%)	5.8% (3.1-8.5%)	6.9% (2.2-11.6%)	3.9% (3.2-4.6)
Italy	1	1.6% (3/185)	2.9% (44/1499)	3.8% (93/2468)	2.5% (39/1568)	3.1% (32/1021)	3.3% (58/1737)	3.3% (58/1759)	3.2% (62/1951)	3.6% (98/2693)	3.8% (98/2586)	3.4% (68/2016)	3.4% (3.1-3.6)
	2	0.7% (0-1.6%)	3.2% (2.3-4.1%)	3.9% (3.1-4.6%)	2.7% (1.9-3.6%)	3.3% (2.1-4.5%)	3.3% (2.4-4.1%)	3.5% (2.6-4.3%)	3.2% (2.4-4%)	3.7% (2.9-4.4%)	3.7% (3-4.4%)	3.3% (2.5-4.1%)	3.4% (3.1-3.6)
Lithuania	1	–	–	9.5% (4/42)	7.4% (2/27)	7.4% (16/215)	3.9% (13/337)	6.5% (22/337)	–	–	4.6% (17/370)	5.5% (27/495)	5.5% (4.5-6.7)
	2	–	–	8.2% (0.1-16.4%)	5.7% (0-13.5%)	9.3% (4.8-13.8%)	4.2% (1.9-6.6%)	6.3% (3.6-9.1%)	–	–	4.6% (2.3-6.9%)	5.8% (3.4-8.2%)	5.8% (4.6-7.0)
The Netherlands	1	2.5% (10/393)	4.8% (17/353)	3.3% (22/671)	3.2% (34/1058)	3.8% (41/1080)	3.2% (12/378)	3.4% (13/387)	4% (32/796)	3.7% (41/1096)	3.6% (43/1189)	3.9% (47/1203)	3.6% (3.2-4.0)
	2	2.7% (1-4.5%)	5.4% (2.9-7.9%)	3.5% (2-4.9%)	3.2% (2.1-4.3%)	3.7% (2.6-4.8%)	3.1% (1.4-4.9%)	3.4% (1.6-5.2%)	4% (2.6-5.3%)	3.6% (2.5-4.7%)	3.5% (2.4-4.5%)	3.8% (2.7-4.9%)	3.6% (3.2-4.0)
Poland	1	N.T.	4.7% (13/275)	5.3% (19/360)	4.3% (13/303)	4.9% (15/307)	6.2% (18/292)	3.7% (11/296)	4.6% (24/521)	4.4% (23/528)	5.9% (54/909)	3.1% (25/797)	4.7% (4.1-5.3)
	2	N.T.	4.1% (1.9-6.3%)	6.0% (3.3-8.7%)	4.3% (2-6.6%)	4.8% (2.4-7.2%)	6.1% (3.3-9%)	3.6% (1.5-5.7%)	4.6% (2.8-6.4%)	4.3% (2.4-6.1%)	5.9% (4.4-7.5%)	2.8% (1.7-4%)	4.6% (4.0-5.3)
Slovenia	1	–	–	–	–	–	–	–	2.4% (21/869)	1.3% (13/1001)	2.6% (32/1245)	2.7% (56/2109)	2.3% (1.9-2.8)
	2	–	–	–	–	–	–	–	2.3% (1.3-3.2%)	1.3% (0.6-1.9%)	2.7% (1.8-3.6%)	2.7% (2-3.4%)	2.3% (1.9-2.8)
United Kingdom	1	2.0% (7/342)	3.5% (18/511)	4.0% (126/3173)	4.0% (97/2434)	3.9% (126/3233)	4.4% (144/3250)	3.8% (186/4854)	3.6% (194/5333)	4.1% (182/4412)	4.5% (128/2819)	4.4% (121/2766)	4.0% (3.8-4.2)
	2	1.7% (0.4-3.0%)	3.4% (1.8-4.9%)	4.1% (3.4-4.8%)	3.9% (3.1-4.7%)	3.9% (3.2-4.6%)	4.3% (3.6-4.9%)	3.8% (3.3-4.4%)	3.5% (3-3.9%)	4.0% (3.4-4.6%)	4.4% (3.7-5.2%)	4.1% (3.4-4.9%)	3.9% (3.7-4.1)
Total	1	3.4 (2.9-4.1)	3.1 (2.7-3.6)	4.1 (3.7-4.5)	3.7 (3.3-4.2)	4.1 (3.7-4.6)	4.1 (3.7-4.6)	3.9 (3.5-4.3)	3.3 (3.0-3.6)	3.7 (3.4-4.0)	3.9 (3.6-4.3)	3.7 (3.4-4.1)	
	2	3.3 (2.8-3.9)	3.1 (2.6-3.5)	4.1 (3.7-4.5)	3.7 (3.2-4.1)	4.1 (3.6-4.5)	4.1 (3.7-4.5)	3.8 (3.5-4.2)	3.2 (2.9-3.5)	3.6 (3.3-3.9)	3.9 (3.5-4.2)	3.6 (3.3-4.0)	

‘–’, no data available; N.T., not tested

Online supplementary Table S2: Results with PPD (1% pet. or included in the TRUE-test[®]) in dermatitis patients obtained in the European Surveillance System on Contact Allergy network 2002-2012, stratified for country, year and sex. Crude percent positive (number of positive reactions/ number of patients tested).

	Gender	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
Austria	M	2.7% (107/3)	0.9% (105/1)	4.4% (86/4)	1.1% (93/1)	5.5% (103/6)	4.5% (42/2)	N.T.	N.T.	N.T.	N.T.	N.T.	3.1% (17/553)
	F	2.7% (107/3)	0.9% (105/1)	4.4% (86/4)	1.1% (93/1)	5.5% (103/6)	4.5% (42/2)	N.T.	N.T.	N.T.	N.T.	N.T.	6.1% (76/1254)
Switzerland	M	– (-/-)	– (-/-)	– (-/-)	– (-/-)	1.2% (85/1)	4.7% (328/16)	2.6% (331/9)	1.3% (151/2)	2.9% (334/10)	2.7% (362/10)	2.5% (272/7)	2.9% (55/1918)
	F	– (-/-)	– (-/-)	– (-/-)	– (-/-)	1.2% (85/1)	4.7% (328/16)	2.6% (331/9)	1.3% (151/2)	2.9% (334/10)	2.7% (362/10)	2.5% (272/7)	5.2% (158/3051)
Germany	M	5.9% (510/32)	2.7% (511/14)	3.1% (464/15)	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	3.4% (72/2142)
	F	5.9% (510/32)	2.7% (511/14)	3.1% (464/15)	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	4.1% (138/3342)
Denmark	M	1.0% (300/3)	1.0% (289/3)	2.4% (246/6)	– (-/-)	– (-/-)	3.1% (222/7)	4.4% (197/9)	2.1% (233/5)	2.3% (255/6)	2.5% (272/7)	– (-/-)	2.2% (46/2060)
	F	1.0% (300/3)	1.0% (289/3)	2.4% (246/6)	– (-/-)	– (-/-)	3.1% (222/7)	4.4% (197/9)	2.1% (233/5)	2.3% (255/6)	2.5% (272/7)	– (-/-)	2.6% (109/4255)
Spain	M	– (-/-)	– (-/-)	7.6% (109/9)	5.8% (113/7)	2.0% (48/1)	0.9% (110/1)	0.0% (47/0)	3.3% (380/13)	3.3% (320/11)	2.2% (317/7)	2.8% (274/8)	3.2% (57/1775)
	F	– (-/-)	– (-/-)	7.6% (109/9)	5.8% (113/7)	2.0% (48/1)	0.9% (110/1)	0.0% (47/0)	3.3% (380/13)	3.3% (320/11)	2.2% (317/7)	2.8% (274/8)	4.8% (182/3807)
Finland	M	– (-/-)	1.3% (74/1)	3.1% (125/4)	1.4% (71/1)	2.3% (85/2)	5.6% (134/8)	4.2% (138/6)	1.6% (124/2)	0.9% (107/1)	2.8% (103/3)	1.7% (57/1)	2.8% (29/1047)
	F	– (-/-)	1.3% (74/1)	3.1% (125/4)	1.4% (71/1)	2.3% (85/2)	5.6% (134/8)	4.2% (138/6)	1.6% (124/2)	0.9% (107/1)	2.8% (103/3)	1.7% (57/1)	4.6% (85/1866)
Italy	M	2.3% (86/2)	1.7% (569/10)	2.8% (864/25)	1.2% (574/7)	2.4% (368/9)	2.0% (600/12)	2.2% (630/14)	2.3% (672/16)	1.9% (884/17)	1.8% (826/15)	1.4% (657/9)	2.0% (136/6866)
	F	2.3% (86/2)	1.7% (569/10)	2.8% (864/25)	1.2% (574/7)	2.4% (368/9)	2.0% (600/12)	2.2% (630/14)	2.3% (672/16)	1.9% (884/17)	1.8% (826/15)	1.4% (657/9)	4.1% (517/12617)
Lithuania	M	– (-/-)	– (-/-)	11.1% (8/1)	0.0% (4/0)	17.4% (38/8)	3.2% (91/3)	7.6% (73/6)	– (-/-)	– (-/-)	6.6% (71/5)	5.4% (88/5)	7.0% (28/401)
	F	– (-/-)	– (-/-)	11.1% (8/1)	0.0% (4/0)	17.4% (38/8)	3.2% (91/3)	7.6% (73/6)	– (-/-)	– (-/-)	6.6% (71/5)	5.4% (88/5)	5.1% (73/1422)
The Netherlands	M	1.9% (156/3)	2.6% (147/4)	1.9% (254/5)	2.6% (405/11)	3.1% (378/12)	2.3% (127/3)	1.4% (137/2)	2.9% (265/8)	3.2% (368/12)	1.7% (397/7)	3.0% (382/12)	2.6% (79/3095)
	F	1.9% (156/3)	2.6% (147/4)	1.9% (254/5)	2.6% (405/11)	3.1% (378/12)	2.3% (127/3)	1.4% (137/2)	2.9% (265/8)	3.2% (368/12)	1.7% (397/7)	3.0% (382/12)	4.2% (233/5509)
Poland	M	– (-/-)	4.3% (88/4)	6.2% (105/7)	6.4% (88/6)	4.3% (88/4)	5.1% (94/5)	1.3% (78/1)	2.2% (174/4)	2.8% (141/4)	4.3% (268/12)	1.0% (189/2)	3.6% (49/1362)
	F	– (-/-)	4.3% (88/4)	6.2% (105/7)	6.4% (88/6)	4.3% (88/4)	5.1% (94/5)	1.3% (78/1)	2.2% (174/4)	2.8% (141/4)	4.3% (268/12)	1.0% (189/2)	5.1% (166/3226)
Slovenia	M	– (-/-)	– (-/-)	– (-/-)	– (-/-)	– (-/-)	– (-/-)	– (-/-)	0.8% (247/2)	0.3% (308/1)	1.0% (396/4)	1.4% (636/9)	1.0% (16/1603)
	F	– (-/-)	– (-/-)	– (-/-)	– (-/-)	– (-/-)	– (-/-)	– (-/-)	0.8% (247/2)	0.3% (308/1)	1.0% (396/4)	1.4% (636/9)	2.9% (106/3621)
United Kingdom	M	1.8% (109/2)	1.7% (169/3)	2.9% (1031/31)	2.6% (783/21)	2.2% (1025/23)	2.7% (1030/29)	2.8% (1579/45)	2.0% (1647/33)	2.7% (1395/39)	2.6% (883/24)	1.9% (859/17)	2.5% (267/10777)
	F	1.8% (109/2)	1.7% (169/3)	2.9% (1031/31)	2.6% (783/21)	2.2% (1025/23)	2.7% (1030/29)	2.8% (1579/45)	2.0% (1647/33)	2.7% (1395/39)	2.6% (883/24)	1.9% (859/17)	4.8% (1062/22350)
Total	M	3.4% (45/1313)	2.0% (40/1992)	3.1% (107/3399)	2.5% (54/2193)	2.9% (66/2292)	3.0% (88/2945)	2.7% (92/3399)	2.2% (88/4088)	2.4% (104/4325)	2.4% (97/4080)	2.0% (70/3573)	
	F	3.4% (80/2319)	3.7% (128/3421)	4.6% (291/6359)	4.4% (180/4127)	4.8% (219/4609)	4.7% (268/5658)	4.5% (291/6452)	3.8% (319/8304)	4.3% (377/8744)	4.7% (402/8555)	4.5% (350/7772)	

‘-’, no data available; N.T., not tested