

***para*-Phenylenediamine: the profile of an important allergen. Results of the IVDK¹**

A. Schnuch, H. Lessmann, P.J. Frosch* and W. Uter†

Information Network of Departments of Dermatology (IVDK) at the University of Göttingen, Von Siebold Str. 3, 37075 Göttingen, Germany

*Department of Dermatology, University of Witten/Herdecke and Klinikum Dortmund gGmbH, Dortmund, Germany

†Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen-Nürnberg, Erlangen, Germany

Summary

Correspondence

Axel Schnuch.

E-mail: aschnuch@med.uni-goettingen.de

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Conflicts of interest

None declared.

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Background *para*-Phenylenediamine (PPD) is an important contact allergen and primarily used in hair dyeing.

Objectives To quantify cases of contact allergy (CA) to PPD attributed to sources of exposure.

Methods Patients with PPD CA, diagnosed by the Information Network of Departments of Dermatology (IVDK; $n = 3307$ of 83 030 patients tested), were divided into five subgroups of exposure. Demographic variables and pattern of concomitant reactions were used to characterize the subgroups further. The impact of individual factors on the risk of PPD CA was examined with a logistic regression analysis. Clinical epidemiology and drug utilization research (CE-DUR) methods were employed to estimate the 10-year prevalence of PPD CA in the general population.

Results The 4% prevalence of PPD CA in patients was extrapolated to a prevalence of 0.96% in the general population. The defined profiles were found to 'explain' the following percentages of PPD CA: (i) hair dyeing in clients 22% (0.2% of the general population); (ii) different occupational exposures, namely hair dyeing by hairdressers, paint- and rubber-associated exposures 23% (0.22% of the general population); (iii) clothing/shoes 12% (0.12% of the general population). A probable causal exposure to PPD could not be identified in about 44% of patients with PPD CA.

Conclusions In more than 50% of cases of PPD CA, a (very) probable causal exposure was identified. In the large remainder (44%) this was not possible. 'Historical' CA without current relevance and active sensitization through patch testing (a further important exposure to PPD) must be considered in these patients.

para-Phenylenediamine (PPD; 1,4-phenylenediamine; CAS 106-50-3) is a colourless intermediate chemical in the production of dyes and antioxidants. PPD or other structurally related compounds are used together with a coupler (e.g. *m*-aminophenol) and an oxidizing agent (e.g. H_2O_2) in hair dyes,¹ but may also occur in leather (e.g. shoes), fur, textiles (e.g. undergarment elastic) or industrial rubber products (e.g. grips of tools or bicycles, tyres, hoses, tubes).² PPD has been recognized as an important contact allergen a long time. For several decades the frequency of sensitization when tested in the standard series, i.e. consecutive patch-test patients, ranged between 4 and 5% [International Contact Dermatitis Research Group (ICDRG) 1967/68 4.9%,³ German Contact Dermatitis Group (DKG) 1988/89 4.9%,⁴ Information Network of Departments of Dermatology (IVDK) 1995/2001 4.2%⁵].

Recently, an increasing frequency of sensitization to PPD has raised concerns, as it may reflect an increasing trend of allergies to hair dyes.⁶ This suspicion is supported by a significant increase in reactions to the hair dye *para*-toluylenediamine (PTD), and in parallel, to the cross-reacting PPD, in clients exposed to hair cosmetics, which we observed between 1995 and 2002,⁷ and which persisted at a high level until 2006.⁸ However, in view of the multitude of potential exposures to PPD and related compounds, the question remains whether or not sensitization to PPD is, above all, due to hair dyeing,⁹ or whether there are other exposures. If so, these need to be identified to target the prevention of PPD contact allergy (CA).¹⁰ We therefore analysed data from patients patch tested with PPD collected by the IVDK in the years 1995–2004, focusing on possible causal exposure.

Methods

The methods used by the multicentre project IVDK (<http://www.ivdk.org>; last accessed 16 May 2008) for epidemiological surveillance of CA have been described in detail elsewhere.^{11–14} For the present analysis all patients patch tested with 1% PPD (pet.) included in the standard series between January 1995 and December 2004 in the IVDK departments complying with the internal quality standards¹⁴ were considered. Patients with more than 10 other positive reactions were excluded from this analysis as putative cases of 'angry back'. Patients were divided into five disjunct subgroups according to their anamnestic and clinical profile (Fig. 1). In addition, based on patch-test reactions at day 3, patients were classified as allergic to PPD (+, ++ or +++) or not allergic (remaining patients).

The demographic and clinical characteristics of the patients are described according to the MOAHLFA index.¹⁵ The frequencies of concomitant positive patch-test reactions at the day 3 reading (as percentage of patients tested) were calculated as crude proportions and as proportions standardized for sex and age,¹⁶ accompanied by the 95% confidence interval (CI) in the patients allergic to PPD. To assess the independent impact of various individual factors on the risk of PPD CA in the clinical sample, a logistic regression analysis was performed. A positive (+ to +++) patch-test reaction to PPD vs. a nonpositive reaction (negative, doubtful or irritant) at day 3 served as outcome. Occupational groups and anatomical sites were aggregated according to reference 17. Clinical epidemiology and drug utilization research (CE-DUR) methods were employed to estimate grossly the 10-year prevalence of PPD CA related to the different exposures in the German general population.^{18,19}

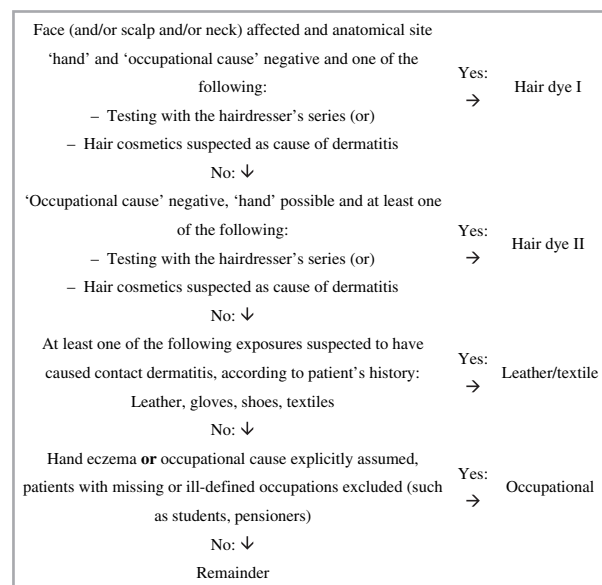


Fig 1. Selection criteria for subgroups allergic to para-phenylenediamine, according to assumed causal exposure and other criteria.

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

Results

Altogether 83 989 patients were patch tested with 1% PPD in petrolatum during the study period, with 3518 positive results. After excluding 959 cases with 'angry back', 83 030 patients remained in the analysis, with 3307 positive reactions (3.98%, 95% CI 3.85–4.12). Important demographic variables in terms of the MOAHLFA index in patients reacting positively to PPD vs. those reacting negatively are shown in Table 1. The former group differed essentially in terms of a higher proportion of occupational cases and cases with hand dermatitis, while face dermatitis was not over-represented in the PPD-positive group.

In the study period, the proportion of patients reacting positively to PPD decreased slightly from 4.7% in 1995 to 4.2% in the following year. Thereafter, the prevalence fluctuated between 3.6% and 4.2%, without a consistent trend, and was 3.8% in 2004.

Characteristics of subgroups

Population characteristics of subgroups

Following the algorithm outlined in Figure 1 patients were allocated to different groups of possible causal exposure. Further details are presented in Table 2. Out of the patients tested, 0.9% were PPD-positive and were grouped in the hair dye subgroups I and II (21.5% of PPD-positive patients), 1.4% were PPD-positive and allocated to the alternative exposure groups 'leather/textile' and 'occupational' (35% of PPD-positive cases), and the remainder ('unspecified'; 43.5% of PPD-positive patients) did not fit into any of the predefined exposure groups. The MOAHLFA index of subgroups largely reflects the selection process. Nevertheless, women were essentially over-represented in the hair dye groups I and II and leg dermatitis was virtually absent,

Table 1 MOAHLFA index of para-phenylenediamine (PPD)-positive vs. PPD-negative patients

		PPD+ (n = 3307)		PPD– (n = 79 723)	
		n	%	n	%
M	Men	1080	32.66	29 823	37.41
O	Occupational	787	23.80	11 225	14.08
A	Atopic eczema	540	16.33	13 648	17.12
H	Site: hand	1129	34.14	21 912	27.49
L	Site: leg	345	10.43	8430	10.57
F	Site: face	452	13.67	11 609	14.56
A	Age 40+	2164	65.44	49 620	62.24

Table 2 Frequencies of sensitization to *para*-phenylenediamine (PPD) (proportion of subjects positive to PPD and of patients tested), MOAHLFA index and 10-year prevalence [according to the clinical epidemiology and drug utilization research (CE-DUR) approach] in different subgroups. (For selection of subgroups see Fig. 1; for calculation of prevalence estimate see Results)

	Subgroup				
	Hair dye I	Hair dye II	Leather/textile	Occupational	Unspecified
No. tested	1910	13 421	8971	15 560	43 168
PPD-positive (n = 3307), n (% of total group tested)	220 (0.3)	491 (0.6)	389 (0.5)	770 (0.9)	1437 (1.7)
% of total cases of PPD CA attributable to profile	6.7	14.9	11.8	23.3	43.5
Grade of reaction (% of positives)					
+	37.3	59.7	52.4	53.1	59.8
++	32.3	28.1	28.0	31.2	30.0
+++ ^a	30.4	12.2	19.5	15.7	10.2
MOAHLFA index of PPD-positive patients in the subgroups (%)					
Men	7.7	20.2	40.9	38.7	35.3
Occupational	0	0	48.3	66.1	6.3
Atopic dermatitis	14.6	17.3	20.6	24.6	10.7
Hand dermatitis	0	4.7	62.7	90.7	11.4
Leg dermatitis	0	0.6	3.9	0.4	22.6
Face dermatitis	35.0	69.5	0.8	2.9	0.6
Age ≥ 40 years	55.9	68.6	58.9	45.7	78.2
CE-DUR 10-year prevalence in the general population (82 000 000) (%)	0.07	0.14	0.12	0.22	0.41

^aSignificant heterogeneity ($P < 0.0001$, χ^2 test) of the distribution of grades of positive reactions across the subgroups and between the first group vs. the remaining groups. CA, contact allergy.

whereas the latter category, together with a high proportion of subjects aged ≥ 40 years, were found in the 'unspecified' group.

Patients in hair dye group I had stronger reactions to PPD (63% ++/+++) significantly more often than all the other groups ($P < 0.0001$, χ^2 test).

Prevalence of *para*-phenylenediamine contact allergy in different subgroups of exposure on a population level

Based on the annual sales data of patch-test materials [supplied by the four main manufacturers present in the German market (Hermal, Reinbeck, Germany; Hal Allergie/Brial, Greven, Germany; Chemotechnique Diagnostics, Malmö, Sweden; Mekos Laboratories Hillerød, Denmark)], the number of applications of the standard series in German patients was calculated for the two 5-year periods (1995–1999 and 2000–2004) as an approximate average of 487 500 and 391 800 patch tests per year, respectively. Based on these figures and after applying the correction factor for a medium case scenario the number of patients with suspected CA eligible for patch testing was 19 960 110 for the 10-year period, i.e. an 'estimated total patch-test population' (for details see refs 18 and 19). The frequencies of PPD CA in the different subgroups found in the analysis of IVDK data (Table 2) were then related to this 'total patch-test population' resulting in the prevalence of PPD CA in different exposure groups at a population level (Table 2).

Concomitant reactions

Concomitant reactions accompanying positive reactions to the index allergen PPD (Table 3) may be due to cross-reactions or to coupled exposure or to both. Reversing the perspective of the well-established association between certain occupations/exposures and an occupation-specific pattern of sensitization,²⁰ the pattern of concomitant reactions not due to cross-reactions may give hints on the exposure to an index allergen.²¹

Hair dye I and II subgroups. The leading allergen in subgroup I is the hair dye PTD, with 75.9% concomitant reactions. In contrast, the symmetrical distribution of reactions to other *para* compounds unrelated to hair dyeing, such as *p*-aminoazobenzene (PAAB), Disperse Orange 3 (DO3), benzocaine and *N*-isopropyl-*N'*-phenyl-*p*-phenylenediamine (IPPD) (Table 3) is indicative of cross-reactions to various degrees. Therefore, the reactions to PTD are very probably due to hair dyeing. The frequent sensitization to *p*-aminophenol and 3-aminophenol, also used in hair dyeing, supports this interpretation. The pattern of concomitant reactions to hair dyes (PTD, *p*-aminophenol) in group II is still increased, albeit not significantly.

'Occupational' and 'leather/textile' subgroups. These subgroups differ strongly from hair dye groups I and II in terms of their pattern of concomitant reactions. The high proportion of PTD (62.9%) as well as the increased sensitization frequency to

Table 3 Pattern of co-sensitization in *para*-phenylenediamine-positive patients to selected allergens, stratified for 'profile' subgroup

	Hair dye I		Hair dye II		Leather/textile		Occupational		Unspecified	
	% pos.	95% CI	% pos.	95% CI	% pos.	95% CI	% pos.	95% CI	% pos.	95% CI
<i>p</i> -Toluylenediamine	75.9	68.9–82.9	47.7	34.3–61.1	40.5	26.9–54.1	62.9	55.2–70.6	50.5	40.5–60.49
<i>p</i> -Aminophenol	43.2	33.1–53.2	24.9	12.3–37.6	10.7	3.9–17.5	18.3	12.0–24.6	17.5	0–35.6
3-Aminophenol	27.8	18.6–36.9	18.6	6.8–30.5	12.2	0–25.9	13.2	5.8–20.6	4.9	0–10.1
'para Compounds' unrelated to hair dyes										
<i>p</i> -Aminoazobenzene	58.3	47.0–69.6	65.9	49.1–82.6	57.4	48.3–66.6	61.4	52.4–70.5	57.0	48.3–65.6
4,4'-Diaminodiphenylmethane	51.4	35.6–67.1	31.2	19.5–42.9	30.7	21.7–39.6	28.0	20.8–35.1	29.9	23.0–36.8
Disperse Orange 3	41.0	27.7–54.3	42.7	31.3–54.0	29.5	20.9–38.2	37.6	27.8–47.5	42.9	31.4–54.5
Benzocaine	18.0	10.0–26.0	12.4	9.0–15.9	9.9	6.9–12.8	12.2	9.7–14.7	18.5	16.2–20.7
IPPD	8.8	2.3–15.3	6.0	3.1–8.9	6.8	4.3–9.3	7.9	6.0–9.8	5.9	4.3–7.6
DPPD	0		2.2	0–6.5	3.4	0.6–6.1	8.9	5.6–12.1	2.1	0–4.3
Allergens unrelated to 'para compounds'										
Ammonium persulphate	3.2	1.2–5.3	9.1	4.0–14.2	16.0	1.9–30.1	35.8	27.4–44.3	24.1	4.1–44.1
Glyceryl monothioglycolate	1.5	0–3.0	5.7	1.3–10.0	17.9	1.6–34.3	29.6	19.9–39.3	4.4	0–9.2
Potassium dichromate	4.3	0–8.8	5.3	3.1–7.5	14.8	11.2–18.4	11.7	9.2–14.1	9.9	8.0–11.8
MDBGN + PE	3.1	0–7.1	4.8	2.9–6.7	5.5	3.2–7.8	7.1	5.1–9.1	4.7	3.4–6.1
MCI/MI	1.3	0–2.6	2.6	1.2–4.0	1.5	0.2–2.7	7.1	5.1–9.1	3.7	2.6–4.9
Colophony	2.4	0.7–4.2	7.0	4.5–9.6	8.8	5.9–11.6	7.3	5.3–9.3	7.1	5.5–8.6
Thiuram mix	7.9	1.0–14.8	1.8	0.6–2.9	11.6	8.2–14.9	6.0	4.2–7.8	4.5	3.2–5.8
Formaldehyde	2.8	0–7.2	3.4	1.5–5.3	4.7	2.5–6.8	3.4	2.0–4.8	2.2	1.3–3.2
Epoxy resin (BADGE)	0.3	0–0.8	2.8	0.6–5.0	1.3	0.2–2.3	3.4	2.0–4.8	1.9	1.1–2.8
<i>p</i> -t-Butylphenol formaldehyde resin	0.4	0–1.1	3.7	1.3–6.1	3.0	1.2–4.8	3.2	1.9–4.5	2.8	1.7–3.8
Mercapto mix (without mercaptobenzothiazole)	0		0.1	0–0.4	4.6	2.3–6.8	1.9	0.9–2.9	2.1	1.1–3.1

Values in bold indicate outstanding results.
 CI, confidence interval; pos., positive; IPPD, *N*-isopropyl-*N'*-phenyl-*p*-phenylenediamine; DPPD, *N,N'*-diphenyl-*p*-phenylenediamine; MDBGN + PE, methylidibromoglutaronitrile + 2-phenoxyethanol (1 : 4); MCI/MI, chloromethylisothiazolinone and methylisothiazolinone (3 : 1), e.g. Kathon™ CG.

other hair cosmetics (ammonium persulphate and glyceryl monothioglycolate) in the occupational group points to hairdressers being sensitized by occupational exposure.^{7,8} Further allergens, namely potassium dichromate, methyl(chloro)isothiazolinone, colophony, epoxy resin, *p*-t-butylphenol formaldehyde and the rubber-associated compounds thiuram mix, mercapto mix and *N,N'*-diphenyl-*p*-phenylenediamine significantly stand out in the occupational and the leather/textile group, indicating exposure to PPD other than in hair dyes. These chemicals can be regarded as typical 'work-related' allergens.^{17,22}

'Unspecified' subgroup. The pattern of co-sensitization is inconclusive, without any outstanding allergen, compared with the other subgroups.

Results of a logistic regression analysis

To assess the independent impact of various factors on the risk of PPD CA in the total study population, a logistic regression analysis was performed. Results are presented in Table 4. Independent significant risk factors for sensitization to PPD were female sex, age ≥ 40 years, occupational background of dermatitis, the anatomical sites head or neck and hand or arm,

and the following occupational groups: hairdressers, construction and related workers, and farmers and related workers. Finally, polysensitization turned out to be a further risk factor for sensitization to an index allergen, as in previous analyses.²³

Discussion

The starting point of this analysis was the hypothesis that the different well-known applications of PPD should be reflected in different subpopulations. Certain criteria, essentially the site of the eczema (face/hand), exposure to, and patch testing with, hair cosmetic ingredients, and 'occupational dermatosis' were used to distinguish different profiles of patients with CA to PPD (Fig. 1). This approach was based on a *a priori* hypothesis (supported by our previous analysis^{7,8}) that in patients sensitized to PPD through hair dyeing, the face (or neck, scalp) would be the predominant site of eczema.^{24,25} An important alternative is occupationally caused hand eczema (e.g. in hairdressers) leading to a distinct subgroup.^{24,26} It is evident from the results of the logistic regression analysis (Table 4) that face dermatitis, hand dermatitis and an occupational cause are independent, if sometimes combined, risk factors for sensitization to PPD. Thus, five distinct subgroups of

Table 4 Results of a logistic regression analysis with positive (+ to +++) vs. nonpositive reaction to *para*-phenylenediamine 1% pet. as outcome, and the explanatory variables listed

	%	OR	95% CI
Female	62.8	1.15	1.05–1.26
Age ≥ 40 years	62.8	1.23	1.13–1.33
Medicolegal evaluation or probable occupational causation	6.7	2.14	1.90–2.41
Anatomical site			
Trunk	15.1	1.00	Reference
Head or neck	19.0	1.39	1.22–1.59
Hand or arm	31.4	1.26	1.10–1.43
Foot or leg	13.8	1.10	0.947–1.27
‘Other’	8.6	1.03	0.86–1.23
Missing	12.1	1.21	0.96–1.31
Occupational group			
Office workers, teachers	15.6	1.00	Reference
Hairdressers, cosmeticians and artists	2.2	3.24	2.69–3.89
Construction workers, stonemasons	1.5	1.52	1.15–2.01
Farmers, animal keepers, florists, etc.	1.6	1.33	1.01–1.76
Textile and leather workers	0.8	1.32	0.92–1.90
Painters, potters, carpenters	1.3	1.29	0.93–1.80
Printers, paper makers	0.4	1.23	0.71–2.14
Service personnel not elsewhere classified	4.4	1.17	0.96–1.42
Chemical industry, plastic material or rubber workers	1.6	1.14	0.85–1.53
Missing job title	6.6	1.11	0.93–1.34
Domestic workers, cleaners	13.8	1.10	0.96–1.26
Metal workers	2.7	1.10	0.86–1.42
Students, pupils, old age pensioners	34.9	1.01	0.89–1.13
Bakers, cooks, butchers, fishmongers	0.7	1.01	0.63–1.62
Electricians, engineers, technicians	3.1	0.91	0.70–1.18
Health service workers	8.8	0.71	0.60–0.85
Polysensitization (number of other positive reactions to standard series)			
0	54.8	1.00	Reference
1	23.7	2.22	2.02–2.45
2	11.8	3.29	2.96–3.66
3	5.5	4.25	3.74–4.84
4 or more	4.2	6.93	6.11–7.85

Effect size estimated by the odds ratio (OR) accompanied by a Wald 95% confidence interval (CI). Hosmer and Lemeshow goodness of fit test: $P = 0.242$.

PPD CA were defined: ‘hair dye I and II’, ‘leather/textile’, ‘occupational’ and a larger subgroup (‘remainder’), containing cases that could not be grouped in one of the previous subgroups (Fig. 1).

Support for the validity of profile definitions by the MOAHLFA index

With regard to the MOAHLFA index, the overall comparison between PPD-positive and -negative patients shows (Table 1) that many of the PPD-positive cases were probably not caused by hair dyes (face dermatitis not increased), and that, alternatively, work-related exposure may be important (occupational: 24% vs. 14% and hand dermatitis: 34% vs. 28%). These descriptive results were confirmed by logistic regression analysis (Table 4). However, considering the subgroups – the MOAHLFA index admittedly being influenced by the selection process – it is remarkable if not surprising that women

predominated by far in the hair dye subgroups (92% and 80%), whereas in the ‘leather/textile’ and ‘occupational’ subgroups, men as well as hand dermatitis were over-represented, as often found in analyses of occupational dermatoses.²⁶ In contrast, a high proportion of leg dermatitis (23%) and age ≥ 40 years (78%) qualifies the ‘unspecified’ subgroup as untypical for either hair dyeing or ‘occupational’. In the hair dye I group, leg dermatitis was virtually absent and patients were younger.

Patterns of concomitant sensitization in specific profiles

In addition to the above observations, the analysis of concomitant reactions found in the five subgroups could further substantiate the validity of the definition of the profiles.²¹ In the present analysis we found patterns of co-sensitization which fit well with the assumed exposure to PPD. In the hair dye groups (I + II), further hair dyes predominate, whereas in the

'leather/textile' group^{27,28} and the 'occupational' group,¹⁷ further sensitizations to several allergens, which remained inconspicuous in the hair dye group, stand out (Table 3). These comprise typical 'work-related' allergens associated with specific exposures.¹⁷ This is reflected in the results of our present logistic regression analysis (Table 4).

The material probably responsible for reactions to PPD

The material that probably caused sensitization to PPD or related compounds (or was the cause of a concomitant reaction to PPD) is evident: hair dyes (*para*-amino compounds) in hairdressers,⁸ and PPD and/or structurally related dyes in textile/leather workers,²⁹ printers³⁰ and painters.^{26,31} Further exposure and sensitization to the dye PPD or the antioxidant IPPD may arise from (mostly occupational) contact with black rubber materials in grips of tools, tyres, hoses or tubes.³² This could explain the increase in reactions to PPD in the group of 'farmers, animal keepers, etc.' and construction workers (Table 4). In previous analyses, sensitization to IPPD was increased in construction workers and in the occupational groups 'farming, etc.' and 'service occupations not classified elsewhere', comprising stock-keepers or transport workers handling tyres.^{17,33} These findings indicate possible unidentified reservoirs of sensitization to PPD-related substances, which eventually cause cross-reactions to PPD.³²

Cross-reactions

Regarding the probable causal material which sensitizes to PPD (or structurally related substances), the impact of cross-sensitization should be considered (Table 3). Cross-reactions or simultaneous reactions in PPD CA to hair dyes and to azo dyes are described to various degrees:^{34–36} frequently (e.g. PTD, PAAB, DO3³⁷; Table 3) or very rarely (e.g. Disperse Blue 106/124³⁸). However, the relationship between PPD and IPPD (the most sensitive marker of the black rubber family³⁹) is ambiguous and seems to be underestimated.¹ While in patients allergic to hair dyes (PPD, PTD) reactions to IPPD were limited (see Table 3),^{35,36,40} IPPD-positive patients reacted to PPD in >30% of cases,^{35,41} showing that primary sensitization to IPPD may contribute to the pool of PPD CA. We have repeatedly noted this 'asymmetrical' pattern of concomitant reactions (*para* compounds,³⁶ chromate/cobalt,³³ fragrances⁴²), and have suggested different potencies and/or doses of the allergens and different conditions of exposure.⁴²

'Non-specific' clinical profile in PPD-positive patients

The pattern of co-sensitization in the 'unspecified' group is, naturally, less conclusive: no allergen emerged significantly, compared with the other subgroups. It cannot be excluded that some or many of these cases of PPD CA were caused by hair dyeing (occupational and nonoccupational), as many people have used hair dyes in the past. For instance, almost 75% of Danish women and 20% of men have dyed their hair at

some point in their lives.⁴³ It is well known that sensitization to PPD can persist for a long time.² Still, alternative exposure (leather/textile and occupational) may have played a role, for which co-sensitization to potassium dichromate and the rubber allergens may be indicative. Therefore, together with the unspecific MOAHLFA index, PPD CA in this particular subgroup may sometimes be an occasional finding of a 'historical' sensitization unrelated to current dermatitis and the current pattern of demographic and clinical data, leaving open the question of causal exposure. The highest average age in the 'nonspecific' group could confirm this notion.

General remarks

In this analysis, the total population found allergic to PPD in the IVDK (n = 3307) was divided into subgroups according to certain criteria (clinical data and patients' history). The criteria were useful, allowing for a probably meaningful designation of the groups, which was further substantiated by analysis of concomitant reactions (surrogate markers of exposure) and by a logistic regression analysis. Analogous to the assessment of clinical relevance of patch-test reactions, where exposure to the allergen has been proven or is at least probable, we would call the relationship between PPD CA and the different distinct exposures 'epidemiologically relevant'. Only the reactions in the 'unspecified' group would be still considered as 'of unknown epidemiological relevance'. In a larger multicentre study from Sweden (n = 21 840) only 20% of PPD CA was found to be related to hair dyeing,¹⁰ which is quite similar to our results (hair dye I+II). Wahlberg *et al.* emphasized that the search for alternative causal exposures should be intensified in order to target prevention.¹⁰

Two particular issues not immediately linked to the question of exposure are: firstly, the strength of the patch-test reaction, and secondly, active (iatrogenic) sensitization as a cause of 'unexplained' PPD CA.

The reactions to PPD were significantly more often stronger (++/+++), and cross-reactions to some *para* compounds tended to be more frequent in hair dye I group than in the other subgroups. We and others have shown that the number of cross-reactions between *para* compounds^{35,37} as well as the number of reactions to unrelated allergens (polysensitization)⁴⁴ increases with the strength of the reaction to an index allergen. In another study a relationship between stronger patch-test reactions to PPD, disease severity and clinical relevance was shown.⁴⁵

Concerning the second point, if active sensitization through patch testing is discussed, PPD is often highlighted as an example.^{2,40,46–49} However, dermatologists disagree on the question of how frequent and how relevant active sensitization to PPD is.^{50–55} A prospective study by the DKG aimed to evaluate late patch-test reactions to PPD. Twenty-one of 1428 (1.5%) patch tested with PPD 1% became positive only after day 7;⁵⁶ while some 'late' reactions (day 7 or beyond) may reflect a peculiar type of individual reactivity, the majority of

late reactions are most likely caused by patch testing,^{53,55–57} proven by an earlier appearance upon re-testing.

In conclusion, sensitization to PPD in a 10-year period was diagnosed in 4% of patients tested. In the general population this would correspond to a 10-year prevalence of PPD CA of 0.96%, according to the CE-DUR estimation. A 10-year prevalence can be regarded as the background frequency of sensitization present in the general population.^{18,58}

Three types of exposure (very) probably leading to PPD CA have been identified: (i) hair dyeing in clients (22% of PPD-positive cases), (ii) occupational exposure (associated with hair dyes, paints and rubber (~23% of PPD-positive patients), and (iii) exposure related to clothing/shoes (~12% of PPD-positive patients).

A causal exposure to PPD could not be identified in ~44% of PPD-positive patients or 1.7% of patients tested (epidemiological relevance uncertain). An unknown part may be 'historical' sensitization without current relevance. The impact of active sensitization through patch testing (obviously a further important exposure to PPD) should not be underestimated. The relatively high proportion of unclassifiable cases of PPD CA is clearly a limitation in our attempt to answer the question: 'What is PPD CA?'

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