

Review Article

Epidemiological data on consumer allergy to *p*-phenylenediamine

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Many women and men now dye their hair. *p*-Phenylenediamine (PPD) is a frequent and important component of permanent hair dye products; exposure to it may cause allergic contact sensitization, acute dermatitis, and severe facial oedema. To increase our understanding of PPD allergy, we reviewed published literature containing PPD patch test data from dermatitis patients and individuals in the general population. This was performed to estimate the median prevalence and the weighted average of PPD sensitization and thereby assess the burden of PPD-containing hair care products on health. Literature was examined using PubMed–MEDLINE, Biosis, and Science Citation Index. The median prevalence among dermatitis patients was 4.3% in Asia, 4% in Europe, and 6.2% in North America. A widespread increase in the prevalence of PPD sensitization was observed among Asian dermatitis patients. In Europe, a decrease in the 1970s was replaced by a plateau with steady, high prevalences ranging between 2% and 6%. The prevalence remained high in North America, although a decreasing tendency was observed. Contact allergy to PPD is an important health issue for both women and men. More stringent regulation and enforcement are required as public health measures to reduce the burden of disease that exposure to PPD has brought to populations.

Key words: contact allergy; epidemics; patch test; PPD; *p*-phenylenediamine. © Blackwell Munksgaard, 2008.

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p-Phenylenediamine (PPD) is a common precursor in oxidative hair dye products. It is an extreme sensitizer that may lead to contact allergy and dermatitis as well as severe facial swellings, which may be mistaken for angioedema. In the late 19th century, a contact allergy epidemic caused by PPD-containing hair care products was recognized (1, 2) and, in response, Sweden and France prohibited the use of PPD (3). Today, within the European Union the Cosmetics Directive currently allows PPD in hair dye products with an upper concentration limit of 6% (3% when added to the oxidising solution required to develop the colour).

Eighteen per cent to 25% of men and 75% of women in Denmark and in the USA have used hair dye products at some point (4–6). In Japan, the prevalence of hair dyeing increased during 1992–2001 among female high school students (14–41%), women in their 20s (6–85%), and men in their 20s (2–33%) (7). PPD is estimated to be present in around 70% of hair dye products

worldwide (8). Thus, exposure to hair dyes (and PPD) is common. To increase our understanding of PPD allergy, we have reviewed published literature containing PPD patch test data from dermatitis patients and individuals in the general population. This was performed to estimate the median prevalence and the weighted average of PPD sensitization and thereby assess the burden to health of PPD-containing hair care products.

Materials and Methods

Literature was examined using PubMed–MEDLINE, Biosis, and Science Citation Index. We aimed to include all scientific articles containing PPD patch test results from the general population and from consecutive patients attending a contact dermatitis clinic. Dermatitis studies from Africa, South America, and Australia were omitted because relatively few were identified (9–12). In general, children were excluded from the analysis,

but in some cases, their patch test results were integrated in published patch test data and, therefore, included in this paper. Search terms included para-phenylenediamine, *p*-phenylenediamine, 4-phenylenediamine, PPD, PPDA, hair dye, oxidative, epidemiology, epidemic, contact allergy, contact sensitization, contact dermatitis, patch test, allergy skin testing, unselected, general population, and healthy. In addition, the databases were searched by the use of the 'related articles' function and by searching the publications by specific authors in the scientific area. Finally, references were localized by the use of reference lists in articles. Although the literature search may not be exhaustive, it probably includes the majority of published articles containing PPD patch test results.

An investigation of the patch test systems showed different suppliers of chambers, strips, tapes, and allergens. The studies can be divided into two general categories according to their patch test methodology: ready-to-apply test systems such as the thin-layer rapid-use epicutaneous test (TRUE test) and traditional standard test series applied in, e.g., Finn[®] chambers. The standard test series concentration of PPD changed over the years, and ingredients differed depending on the country of origin (e.g. Indian, Chinese, and Italian). When possible, PPD test concentrations have been identified and presented in this paper. Figures 1–3 were based entirely on studies using 1% PPD in petrolatum (pet.); other studies using higher or lower concentrations were excluded. When patch test results straddled more than one year, the median year was considered representative (e.g. when 1972–1974 was indicated, 1973 was designated as the representative year). The calculated median prevalence and weighted average were based on studies using 0.1%, 0.5%, 1%,

and 2% PPD in pet. In cases where the size of the study population was given as an interval, e.g. 900–2000 (13), the study was omitted from the calculations.

To clarify the term 'epidemic', the authors mean the occurrence of cases of an illness in a community or region, which is in excess of the number of cases normally expected for that disease in that area at that time (14).

Results

Tables 1–3 show PPD patch test results from consecutive dermatitis patients in Asia, Europe, and North America. The median prevalence among dermatitis patients was 4.3% in Asia, 4% in Europe, and 6.2% in North America. The weighted average was 4.4% in Asia, 4.1% in Europe, and 6.0% in North America. The general trend of these analyses was not affected when studies using 0.1%, 0.5%, and 2% PPD were excluded. The median prevalence for men and women was 3.3% and 3.1% in Asia and 4.3% and 4% in Europe, respectively. The weighted average was also higher among men (4.7%) than among women (3.5%) in Asia, whereas more women (3.9%) than men (3.6%) were sensitized in Europe. Sex analysis was not performed in studies from North America due to insufficient data.

Figure 1 shows a widespread increase in the prevalence of PPD sensitization among Asian dermatitis patients since 1984. From the 1990s until the present day, sensitization prevalences have ranged between 2% and 14%. Figure 2 shows the PPD sensitization prevalence among dermatitis patients in Europe. Apparently, a decrease in the 1970s has been replaced by a plateau with steady, high prevalences ranging between 2%

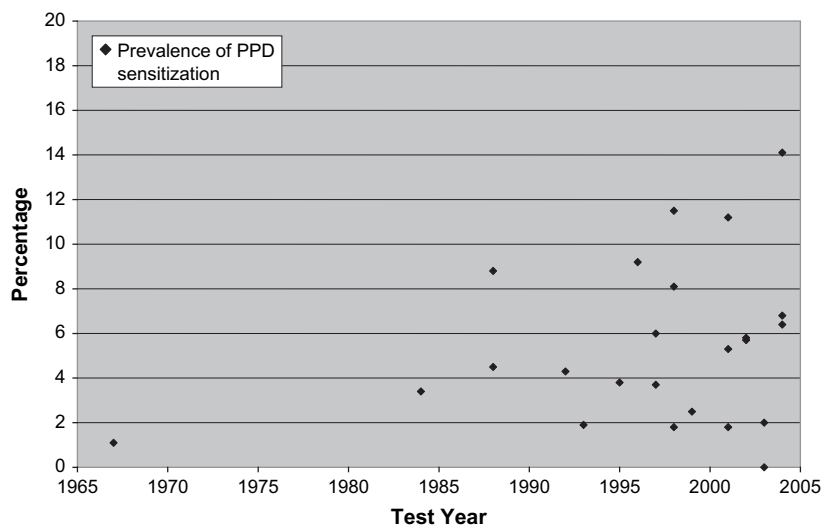


Fig. 1. The prevalence of positive patch test reactions to PPD (1% in pet.) among Asian patch test populations. Pet., petrolatum; PPD, *p*-phenylenediamine.

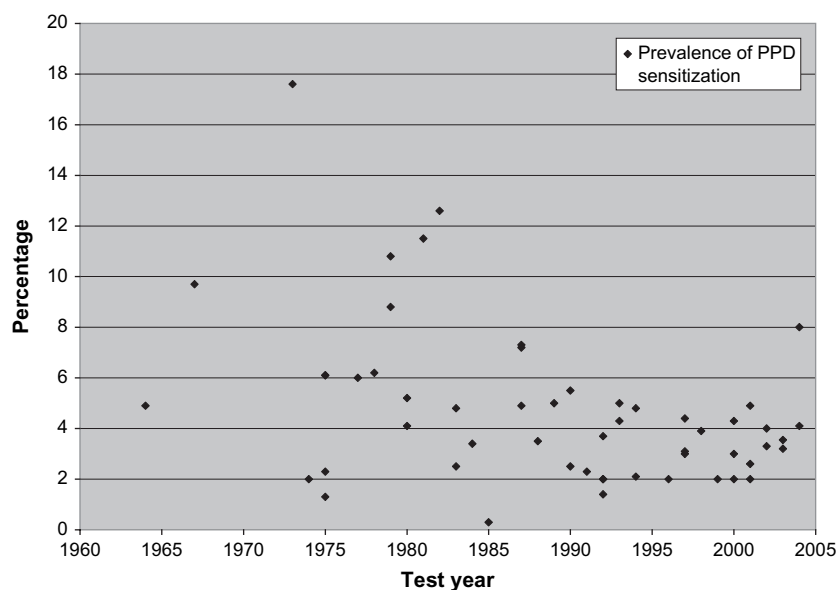


Fig. 2. The prevalence of positive patch test reactions to PPD (1% in pet.) among European patch test populations. Pet., petrolatum; PPD, *p*-phenylenediamine.

and 6%. Despite a decreasing tendency, PPD sensitization prevalences are generally higher in North America than in Europe (with the majority ranging between 4% and 7%) (Fig. 3). Table 4 shows PPD sensitization prevalence in general populations from Europe, Thailand, and Australia. The highest estimate was identified in a Thai population (2.7%), whereas in one other study, no cases were identified in, e.g., the first Glostrup study from 1990. The median prevalence and weighted average of PPD sensitization in the general population were 0.3% and 1.0%, respectively.

The majority of patch test populations were tested with the standard test series. TRUE tests were only used in a few dermatitis populations in Europe and Asia and never reported from centres in North America. In the general popu-

lations, TRUE tests were used in 6 (35%) of 17 studies. No significant differences regarding age and sex were identified between the patch test populations in Asia, Europe, and North America. Finally, patch readings were only rarely performed on D7 in Asian patch test populations compared with European and North American test populations.

Discussion

This study shows the development of contact allergy prevalences to PPD on three different continents (Figs 1–3). The weighted prevalence average was 4.4% in Asia, 4% in Europe, and 6% in North America. These estimates did not differ much from their corresponding median

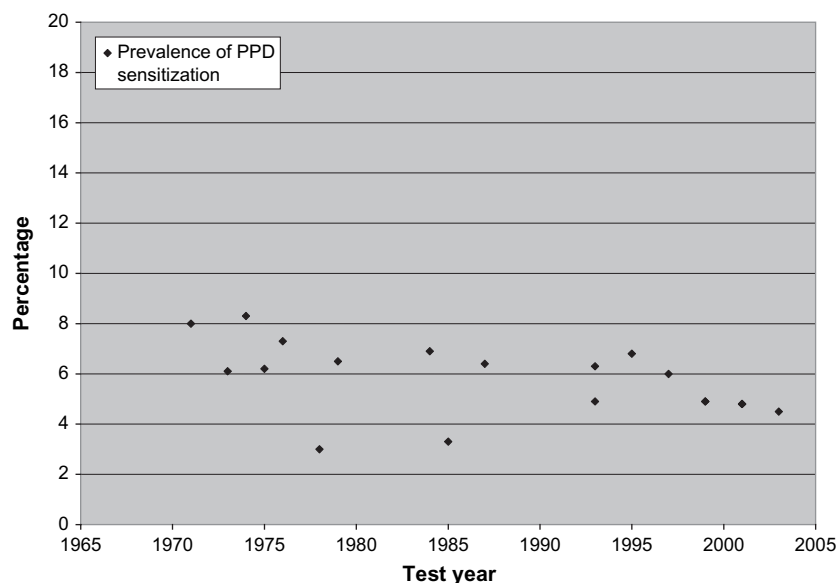


Fig. 3. The prevalence of positive patch test reactions to PPD (1% in pet.) among North American patch test. Pet., petrolatum; PPD, *p*-phenylenediamine.

Table 1. Patch test data from Asian dermatitis populations

Author	Study period*	City	Country	n	Mean age or year interval (years)	Age >40 years (%)	Female/male (%)	Patch test material	PPD test concentration (%)	Patch test reading performed on days	Positive reaction to PPD total (%)	Positive reaction to PPD female (%)	Positive reaction to PPD male (%)
Kanan (50)	1966–1969	Kuwait City	Kuwait	1473	35–55	—	—	Four-layer gauze	1	2, 3	1.1	—	—
Hirano and Yoshikawa (51)	1976–1979	Nagoya	Japan	434	—	—	—	Standard series	0.1 and 0.6	2, 3	3.2	—	—
Goh (52)	1984–1985	Singapore	Singapore	2471	32	—	46.9	Standard series	1	2, 4	3.4	3.1	3.6
Lim et al. (53)	1986–1990	Singapore	Singapore	5557	—	—	52.6	Standard series	1	2, 4	4.5	—	—
Lee and Lam (54)	1986	Hong Kong	China	88	32.2	—	62.5	Standard series	0.5	2, 3	0	0	0
Lee and Lam (55)	1987–1988	Hong Kong	China	437	—	—	—	Standard series	0.5	2, 4	0.2	—	—
Fan and Zhao (46)	1988–1989	Nanjing	China	204	15–59	—	66.1	Standard series	—	2–4	8.8	—	—
Zhang et al. (56)	1989	Beijing	China	124	—	—	—	Standard series	0.5	2, 3	16.1	—	—
Liu et al. (57)	1988–1996	Nanjing	China	1135	34.3	—	72.5	Standard series	0.5	2–4	8	—	—
Lestringant et al. (58)	1989–1996	Al Ain	United Arabs	373	4–87	—	61.6	Standard series and TRUE test	†	2, 3	4.3	3	6.3
Wang et al. (59)	1992–1993	Shanghai	China	88	33	—	85	Standard series	—	—	0	0	0
Akasya-Hillenbrand and Ozkaya-Bayazit (60)	1996–1999	Istanbul	Turkey	542	33.5	—	55.9	Standard series	1	2–5	3.7	4.2	2.9
Akyol et al. (61)	1992–2004	Ankara	Turkey	1038	33.4	30	67.9	Standard series	1	2, 4	1.8	1.2	3
Okrasinski and Gul (62)	1993–1994	Khamis Mushayt	Saudi Arabia	100	—	30	52	TRUE test	†	3	3	1.9	4.2
el-Rab and al-Sheikh (63)	1995*	Riyadh	Saudi Arabia	240	12–75	—	54.5	Standard series	1	2, 3	3.8	3.1	4.6
al-Sheikh and Gad el-Rab (64)	1996*	Riyadh	Saudi Arabia	271	12–75	—	54.2	Standard series	—	2, 3	9.2	3.9	5.3
Lam et al. (65)	1995–1999	Hong Kong	China	2585	—	—	59.3	Standard series	1	2, 4	6	5	7.3
Sharma and Chakrabarti (47)	1998*	Chandigarh	India	200	39.8	—	39	Standard series	1	2, 3	11.5	10.3	12.3
Chan et al. (26)	1998–1999	Singapore	Singapore	406	53	—	—	Standard series	1	3	8.1	—	—

(Continued)

Table 1. Continued

Author	Study period*	City	Country	n	Mean age or year interval (years)	Age >40 years (%)	Female/male (%)	Patch test material	PPD test concentration (%)	Patch test reading performed on days	Positive reaction to PPD total (%)	Positive reaction to PPD female (%)	Positive reaction to PPD male (%)
Freireich-Astman et al. (66)	1999–2000	Tel Aviv	Israel	943	42	—	59	Standard series	1	2, 3	2.5	3.1	1.8
Lazarov (67)	1998–2004	Tel Aviv	Israel	2156	45.4	—	67.8	Standard series	1	2, 3	1.8	—	—
Singhal and Reddy (68)	2000*	New Delhi	India	75	—	—	—	Standard series	0.1	2, 3	1.3	0	2.6
Wang et al. (48)	2001–2003	Beijing	China	240	40.5	44.2	—	Standard series	1	2, 3	5.8	—	—
Akhtar et al. (69)	2000–2003	Dhaka	Bangladesh	340	—	—	57.4	Standard series	—	2, 3	11.2	—	—
Hussain et al. (70)	2002†	Lahore	Pakistan	350	33.8	—	66.9	Standard series	1	2–4	5.7	3.8	9.5
Kashani et al. (71)	2002–2004	Teheran	Iran	250	32.7	26	76	Standard series	1	2–4	2	1.6	3.3
Onder and Oztas (72)	2003*	Ankara	Turkey	272	>56	—	63.6	Standard series	1	4	9.9	—	—
Sharma et al. (73)	2004*	New Delhi	India	220	11–70	50	41.4	Standard series	1	—	6.4	5.5	3.1
Magen et al. (74)	2002–2005	Ashkelon	Israel	864	—	45.3	63.3	TRUE test	†	2, 3	0.1	—	—
Li et al. (75)	2004*	Beijing	China	217	43	—	61.8	Standard series	—	2, 3	6.8	—	—
Li et al. (76)	2003–2005	Beijing	China	599	39.9	—	71.5	Standard series	—	2, 3	14.1	—	—
Bajaj et al. (77)	1997–2006	Allahabad	India	1000	35.9	—	56.6	Standard series	1	2, 4	5.3	—	—

—, not given; PPD, *p*-phenylenediamine; TRUE, thin-layer rapid-use epicutaneous test.

*If study period was not given, the year of publication has been inserted instead.

†The TRUE test contains 0.073 mg PPD/patch.

Table 2. Patch test data from European dermatitis populations

Author	Study period*	City	Country	n	Mean age or year interval (years)	Age >40 years (%)	Female/male (%)	Patch test material	PPD test concentration (%)	Patch test reading performed on days	Positive reaction to PPD total (%)	Positive reaction to PPD female (%)	Positive reaction to PPD male (%)
Skog and Thyresson (78)	1948–1951	Stockholm	Sweden	3287	—	—	—	Standard series	2	2, 4	4.3	5.1	3.4
Modée (79)	1958–1961	Stockholm	Sweden	2903	—	—	—	Standard series	2	2, 4	10.6	11.1	9.8
Marcussen (80)	1938–1955	Copenhagen	Denmark	36 000	—	—	—	Standard series	2	—	1	—	—
Magnusson et al. (81)	1968*	Six centres	Sweden, Denmark, Norway	5558	—	—	57	Standard series	2	—	4.5	3.5	5.3
Oleffe et al. (82)	1967–1968	Brussels	Belgium	300	—	—	—	Standard series	1	—	9.7	4.3	13
Rudzi and Kleniewska (83)	1967–1970	Warsaw	Poland	612	—	49.1	—	Standard series	2	—	12	13.6	11.6
Brun (84)	1968–1974	Geneva	Switzerland	1000	—	—	—	Standard series	2	2–4	5.9	—	—
Brun (85)	1975–1981	Geneva	Switzerland	1170	—	—	—	Standard series	0.5	2–4	4.7	—	—
Lämmer (86)	1970–1975	Berlin	Germany	1008	—	—	—	Standard series	1	2, 3	17.6	—	—
Romaguera and Grimalt (87)	1973–1977	Barcelona	Spain	4600	—	—	—	Standard series	1	—	6.1	—	—
Hammershoy (88)	1973–1977	Odense	Denmark	3225	45.4	—	55	Standard series	1	2, 3	1.3	1	0.3
Panconesi et al. (89)	1975*	Florence	Italy	688	—	—	—	Standard series	—	—	2.3	—	—
Stransky and Krasteva (90)	1975–1987†	Sofia	Bulgaria	1237	—	—	46	—	1	—	8.52–14.46	—	—
Hussain (91)	1970–1973	Glasgow	Scotland	1312	12–74	—	54	Standard series	2	2, 4	4	—	—
Camarasa (92)	1977	Nine centres	Spain	30 873	—	—	56.1	Standard series	1	3, 5	9.9‡	—	—
Calas et al. (93)	1978*	Marseilles	France	500	—	—	—	Standard series	2	—	6.2	—	—
Lachapelle and Tennstedt (94)	1979*	Brussels	Belgium	400	—	—	43.8	Standard series	1	2, 4	8.8	8	9.3
Korossy et al. (95)	1979	Budapest	Hungary	436	—	—	56	Standard series	1	2, 3	10.8	12.4	9
Fregert et al. (34)	1964–1965	Seven centres	§	4825	—	—	—	Standard series	1	2–4	4.9	4.5	5.5
Gollhausen et al. (96)	1977–1983	Munich	Germany	11 962	—	—	60	Standard series	1	2, 3	4.1	3.9	4.3
Dooms-Goossens (97)	1978–1985	Leuven	Belgium	6818	38	—	64	Standard series	—	2–4	12.6	—	—
Edman and Møller (98)	1980	Lund	Sweden	—	—	—	—	Standard series	—	2, 3	5.2	3.7	7.9

(Continued)

Table 2. Continued

Author	Study period*	City	Country	n	Mean age or year interval (years)	Age >40 years (%)	Female/male (%)	Patch test material	PPD test concentration (%)	Patch test reading performed on days	Positive reaction to PPD total (%)	Positive reaction to PPD female (%)	Positive reaction to PPD male (%)
Vestey et al. (99)	1982–1985	Edinburgh	Scotland	496	♂ = 45; ♀ = 37	—	61.1	Standard series	1	2, 5	4.8	4	12
Young and Houwing (100)	1974	Utrecht	The Netherlands	250	—	—	54	Standard series	1	2	2	—	—
Young and Houwing (100)	1984	Utrecht	The Netherlands	614	—	—	67.8	Standard series	1	2	3.4	—	—
Sertoli et al. (101)	1984–1993	GIRDCA	Italy	42 839	—	—	—	Standard series	0.5/1 [†]	2–4	3.5	—	—
Guerra et al. (102)	1985–1990	Bologna	Italy	261**	43.3	—	98.1	Standard series	0.5	2, 3	7.3	—	—
Christophersen et al. (103)	1985–1986	Seven centres	Denmark	2166	—	—	67.8	Standard series	0.5	2, 3	0.3	0.2	0.4
Broeckx et al. (104)	1987*	Brussels	Belgium	5202	—	—	64	Standard series	—	—	7.2	—	—
Enders et al. (105)	1987	Munich	Germany	1845	—	—	62.9	Standard series	1	2, 3	4.9	5.0	4.7
Bruckner-Tuderman et al. (106)	1989	Zurich	Switzerland	921	42.8	—	59	Standard series	—	2–4	5	5	5
Bangha and Elsnér (107)	1990–1994	Zurich	Switzerland	5565	—	—	57.6	Standard series	1	2–4	3.7	3.4–5.7	2–4
Shehade et al. (108)	1991*	Manchester	England	4721	—	—	—	Standard series	—	2, 4	2.3	—	—
Monk (109)	1993–1996	Bedford	England	753	—	—	—	Standard series	1	2, 7	2.1	—	—
Castiglioni et al. (110)	1992	Turin	Italy	834	—	—	75.5	Standard series	—	2, 4	2	—	—
Uter et al. (111)	1992–1996	IVDK	Germany, Austria, Switzerland	45 250	—	—	—	—	—	—	4.3–5.4	—	—
Schnuch et al. (112)	1990–1995	IVDK	Germany, Austria, Switzerland	36 491	—	55.9	64.8	Standard series	1	3	5	5.1 ^{††}	4.3 ^{††}
Hoeller et al. (18)	1980–1986	Aachen	Germany	3606	—	—	60.5	Standard series	1	2–4	2.5	2.3	2.7
Hoeller et al. (18)	1987–1993	Aachen	Germany	3304	—	—	60.5	Standard series	1	2–4	5.5	5.0	6.0
Hoeller et al. (18)	2004	Aachen	Germany	201	—	—	60.5	Standard series	1	2–4	8	—	—
Devos and Van (33)	1992–1994	Nijmegen	The Netherlands	678	14–79	—	62	Standard series	1	2, 3	4.3	—	—
Devos and Van (33)	1995–1999	Nijmegen	The Netherlands	2058	—	—	—	Standard series	1	2, 3	3.1	—	—
Koopmans and Bruynzeel (113)	1996–1999	Amsterdam	The Netherlands	2375	—	—	—	Standard series	—	2, 3, 6, 7	3	—	—

(Continued)

Table 2. Continued

Author	Study period*	City	Country	n	Mean age or year interval (years)	Age >40 years (%)	Female/male (%)	Patch test material	PPD test concentration (%)	Patch test reading performed on days	Positive reaction to PPD total (%)	Positive reaction to PPD female (%)	Positive reaction to PPD male (%)
Kränke et al. (114)	1992–1993	Fourteen centres	Austria	11 544	39.5	—	71.5	Standard series	1	2, 3	2	—	—
Heine et al. (115)	1995–2002	IVDK	Germany	7408	60–66	—	61.7	Standard series	1	3	4.4	—	—
Serra-Baldrich et al. (116)	1995*	Barcelona	Spain	800	33	—	68	Standard series	0.6	2, 4	2.9	—	—
Armstrong et al. (117)	1982–1998	London	England	26 706	—	—	59	Standard series	**	—	2.5	—	—
Britton et al. (118)	2000	Seven centres	England	3062	—	—	—	—	1	2, 4	3	—	—
Lindberg et al. (16)	1991–1993	Nine centres	Sweden	3680	—	48.3	64.7	Standard series and TRUE test	—	2–4	1.4	1.3**	0.9**
Lindberg et al. (16)	1999–2001	Nine centres	Sweden	3790	—	51.3	63.2	Standard series and TRUE test	1	2–4	2.8§	2.2**	1.3**
Bruynzeel et al. (119)	1996–2000	—	Ten European centres	26 210	—	—	54.3–71.4	TRUE test Standard series and TRUE test	1	2–4	3.9	4.3	3.2
Geier et al. (120)	1999–2001	IVDK	Germany, Austria, Switzerland	25 451	—	—	—	—	1	—	4.3	—	—
Hasan et al. (19)	1995–1997	Seven centres	Finland	9373	—	—	—	Standard series	—	2, 4, 5, 7	2	—	—
Hasan et al. (19)	2000–2002	Seven centres	Finland	11 784	—	—	—	Standard series	—	2, 4, 5, 7	2	—	—
Machovecova et al. (121)	1997–2001	Nine centres	Czech Republic	12 058	41.7	—	63.4	Standard series	1	2, 3	2	2.2	1.7
Hansen and Kroon (122)	2001–2002	Stavanger	Norway	857	38.3	—	64	Standard series	1	2, 3	2.6	3	2
Patel et al. (15)	1999–2004	London	England	6177	—	—	—	Standard series	1	2–5	4.9**	5.3	4.1
Rudzi and Rebandel (20)	2000–2006	Warsaw	Poland	7125	—	—	71	Standard series	—	—	3.6	3.1	4.8
Worm et al. (123)	2001–2004	IVDK	Germany, Austria, Switzerland	30 740	—	63.8–69.9	61.7	Standard series	1	2–4	4	—	—
Uter et al. (124)	2002–2003	EESCA	Nine European countries	9140	—	57.8	62.9	Standard series and TRUE test	1	3, 5***	3.3	—	—
Uter (125)	2004	EESCA	Eleven European countries	9905	—	57.3	65.2	Standard series and TRUE test	1	3–5***	4.1	—	—

(Continued)

Table 2. Continued

Author	Study period*	City	Country	n	Mean age or year interval (years)	Age >40 years (%)	Female/male (%)	Patch test material	PPD test concentration (%)	Patch test reading performed on days	Positive reaction to PPD total (%)	Positive reaction to PPD female (%)	Positive reaction to PPD male (%)
Hillen et al. (23)	2003–2004	Nine centres	Germany	1428	—	—	—	Standard series	1	1–3, 7, 14, 21	3.2	—	—
Uter et al. (126)	2003–2006	IVDK	Germany, Austria, Switzerland	394 ^{†††}	Median = 49	66.8	—	Standard series	1	3–5 ^{***}	20.3 ^{††}	—	—
Thyssen et al. (17)	1985–2007	Gentofte	Denmark	16 229	47.8	—	64.1	Standard series	0.5/1 [§]	2–4, 7	2.0	2.2	1.7

—, not given; EESCA, European Surveillance System on Contact Allergies; GIRDCA, Gruppo Italiano Ricerca Dermatiti da Contatto; IVDK, Information Network of Departments of Dermatology; PPD, *p*-phenylenediamine; TRUE, thin-layer rapid-use epicutaneous test.

*If study period was not given, the year of publication has been inserted instead.

[†]Sensitization rates registered in 1975, 1978, 1981, 1984, and 1987.

^{††}92/278 (33.1%) were considered occupational. If these are left out of the analysis, the PPD sensitization rate was 6%.

[§]Denmark, Finland, Germany, Italy, Holland, Sweden, and England.

[¶]0.5% PPD was used between 1984 and 1988. One per cent PPD was used from 1989.

**Hairdressers' clients.

^{††}Standardized.

^{†††}Armstrong et al. presented a steady rate of PPD sensitization during the period. PPD dihydrochloride 0.5% in petrolatum was used during 1985–1988. If these years are excluded from the analysis, 3.2% was sensitized to PPD between 1989 and 1998.

^{§§}Increase between 1991–1993 and 1999–2001 was significant ($P < 0.05$).

^{¶¶}Patel et al. demonstrated an increase from 3.6% in 1999 to 7.1% in 2004.

^{***}Application time was mostly 2 days but some centres only applied for 1 day.

^{††††}Patients who had been exposed to hair cosmetics but never worked as hairdressers.

Table 3. Patch test data from North American dermatitis populations

Author	Study period*	City	Country	n	Mean age or year interval (years)	Age >40 years (%)	Female/ male (%)	Patch test material	PPD test concentration (%)	Patch test reading performed on days	Positive reaction to PPD total (%)	Positive reaction to PPD female (%)	Positive reaction to PPD male (%)
Baer et al. (49)	1937	New York	USA	—	—	—	—	Standard series	2	—	5.6	—	—
Baer et al. (49)	1961–1962	New York	USA	—	—	—	—	Standard series	2	—	14	—	—
Epstein et al. (127)	1963–1966	San Francisco	USA	440	—	—	—	Standard series	2	2, 4, 7	7.3	—	—
Baer and Ramsey (128)	1968–1970	New York	USA	540	—	—	—	Standard series	2	—	13.5	—	—
Kanof and Biondi (129)	1970–1974	New York	USA	538	—	—	—	Standard series	2	—	11	—	—
Lepine (130)	1973–1975	Fort Jackson	USA	131	—	—	—	—	1	2, 4	8.3	—	—
Rudner (13)	1970–1972	NACDG	USA and Canada	1200	—	—	—	Standard series	1	—	8	—	—
Rudner et al. (131)	1972–1974	NACDG	Canada and USA	2917	—	—	—	Standard series	1	—	6.1	—	—
Rudner (13)	1975–1976	NACDG	Canada and USA	900–2000	—	—	—	Standard series	1	—	6.2	—	—
Lynde et al. (132)	1972–1981	Vancouver	Canada	4190	—	—	—	Standard series	1	2, 4	7.3	8	6.2
Nethercott (133)	1977–1979	Toronto	Canada	200	—	—	—	Standard series	1	2, 4	3	—	—
Taylor (132) [†]	1979–1980	NACDG	Canada and USA	1753–2145	—	—	—	—	1	—	6.5	—	—
Hogan et al. (134)	1983–1987	Saskatoon	Canada	542	39.4–41.4	—	61	Standard series	—	2–4	3.3	4.0	2.4
Storrs et al. (135)	1984–1985	NACDG	Canada and USA	1138	42.9	—	55.9	Standard series	1	2, 3	6.9	—	—
Nethercott et al. (136)	1985–1989	NACDG	USA and Canada	4055	43.8	—	57	Standard series	1	2, 3, 5, 7	6.4	—	—
Albert et al. (137)	1990–1997	Boston	USA	608	44.5	—	69.9	Standard series	1	2, 3	4.9	5.6	3.3
Marks et al. (138)	1992–1994	NACDG	Canada and USA	3549	46	—	62	Standard series	1	2–4, 7	6.3	—	—
Marks et al. (139)	1994–1996	NACDG	Canada and USA	3111	47	—	62	Standard series	1	2–4, 7	6.8	—	—
Marks et al. (140)	1996–1998	NACDG	Canada and USA	3441	3–96	—	—	Standard series	1	2–4, 7	6	—	—
Marks et al. (141)	1998–2000	NACDG	Canada and USA	5831	3–95	—	—	Standard series	1	2–4, 7	4.9	—	—
Wetter et al. (142)	1998–2000	Mayo Clinic ^{††}	USA	1320	54.7	—	65.6	Standard series	1	2–4, 7	4.9	—	—
Mohammad et al. (143)	2000–2003	New York	USA	103	—	—	—	Standard series	1	—	4.8	—	—
Pratt et al. (144)	2001–2002	NACDG	USA	4913	2–97	—	—	Standard series	1	2–4, 7	4.8	—	—
Davis et al. (145)	2001–2005	Mayo Clinic ^{††}	USA	3832	55.1	—	66.8	Standard series	1	2–4, 7	4.5	—	—

—, not given; NACDG, North American Contact Dermatitis Group; PPD, *p*-phenylenediamine.

*If study period was not given, the year of publication has been inserted instead.

†Numbers identified in Lynde et al. are presented. This article states that J. Taylor is the responsible author and compiled the data for publication. However, this publication has not been identified.

††Mayo Clinic has locations in Rochester, MN, USA; Jacksonville, FL, USA; and Phoenix and Scottsdale, Ariz.

Table 4. Patch test data from studies performed in the general population

Author	Study period*	City	Country	Population	n	Age (years)	Female/male (%)	Patch test material	Patch test concentration (%)	Patch test reading performed on days	Positive reaction to PPD (%)	Positive reaction to PPD female (%)	Positive reaction to PPD male (%)
Sipos (146)	1967*	—	Hungary	Subjects with intact skin	659	—	—	Standard series	2	3	1.6	—	—
Forsbeck et al. (147)	1968*	Stockholm	Sweden	Twins	202	43–82	83.1	Standard series	2	3	1	1.2	—
Magnusson and Moller (148)	1968–1977	Lund	Sweden	Patients awaiting hip surgery	274	Mean = 65	60	Standard series	1	3	0.7	1.2	0
Seidenari et al. (149)	1990*	Modena	Italy	Cadets	593	18–28	—	Standard series	1	3	0.5	—	0.5
Nielsen and Menné (150)	1990	Glostrup	Denmark	General population	567	15–69	49.2	TRUE tests	†	2	0	0	0
Schafer et al. (151)	1994–1995	Augsburg	Germany	General population	1141	28–78	50.4	Standard series	1	3	1.2	—	—
Mortz et al. (152)	1995–1996	Odense	Denmark	School children	1146	12–16	54.1	TRUE tests	†	3*	0.2	0.2	0.2
Bryld et al. (153)	1996	—	Denmark	Twins [§]	627	20–44	62.3	TRUE tests	†	3	0	0	0
Nielsen and Menné (150)	1998	Glostrup	Denmark	General population	469	15–41	58.8	TRUE tests	†	2	0.2	0	0.5
Greig et al. (154)	2000*	—	Australia	General population	219	18–82	61	Standard series	1	2, 3	0	0	0
Schnuch et al. (155)	1992–2000	—	Germany	General population [¶]	—	All ages	—	Standard series	1	3	1.6	—	—
Thyssen et al. (156)	2001–2005	—	Denmark	General population [¶]	—	All ages	—	Standard series	1	3	0.4	—	—
Spiewak (157)	2002	—	Poland	Students	135	18–19	54.1	Standard series	—	2	0	0	0
Svedman et al. (158)	2003–2004	Karlskrona	Sweden	Elderly stented persons	484	Mean = 67	21.2	Standard series	0.25	3, 7	0	0	0
White et al. (159)	2004	Bangkok	Thailand	Adult volunteers	2545	18–55	61.5	Standard series	1	2	2.7	3.2	2.4
Lerbaek et al. (160)	2005–2006	—	Denmark	Twins [§]	270	29–55	66.3	TRUE tests	†	3	0	0	0
Dotterud and Smith-Sivertsen (161)	2007*	Tromsø	Norway	General population	1236	18–69	55.8	TRUE tests	†	3	0.3	0.3	0.4

—, not given; PPD, *p*-phenylenediamine; TRUE, thin-layer rapid-use epicutaneous test.

*If study period was not given, the year of publication has been inserted instead.

†The TRUE test contains 0.073 mg PPD/patch.

‡Forty children were not read at D3 but rather on D2, D4, or D7. Some were also read by parents who had been previously instructed.

§Calculations made on subjects without hand eczema.

¶A general population estimate is calculated through the clinical epidemiology and drug utility research method.

prevalences. In Europe, high levels of PPD sensitization were observed in the 1970s. A lower, and apparently stable, plateau with prevalences ranging between 2% and 6% has since been reached. Individual patch test centres in England (15), Sweden (16), Denmark (17), and Germany (18) have recently demonstrated increasing prevalences of PPD sensitization. However, data from Finland (19) and Poland (20) have not shown any increase. PPD sensitization is still common in Europe. Sex analysis showed that more women than men were PPD sensitized. This is in accordance with a higher exposure of hair dyes in women in Europe (5).

A higher weighted prevalence average of PPD sensitization was identified in North America with 4–7% patients sensitized to PPD. However, a steady decrease has been observed since the 1970s and further studies will show whether this trend is maintained. We were not able to explain the high prevalence in North America, but we speculate that it may be a result of large African-American and Hispanic-American populations (who may tend to opt for darker shades of hair dye) or simply a result of different hair dyeing habits. Alternatively, there may be different patient selection criteria for patch testing in North America owing to different health care systems.

In Asia, the literature documents evidence of an epidemic of contact allergy to PPD. Sensitization prevalences ranged between 2% and 12% with numerous studies performed in recent decades. The weighted prevalence average showed that the prevalence of PPD sensitization was higher in Asian men than in women. This may be partly explained by different cultural practices, such as dyeing grey facial hair. Facial hair needs to be dyed more often than scalp hair, perhaps increasing the risk of sensitization. Also, it seems plausible that darker shades of hair dye would be more popular in Asia than lighter shades. Finally, it is possible that more concentrated forms of PPD dye are used as a result of insufficient adherence to instructions when mixing powdered PPD.

The PPD prevalences identified in Asia may be conservative estimates as no clinics document performing late patch readings. It has been demonstrated previously that D6/D7 readings may identify additional patients sensitized to PPD (17, 21, 22). However, it has also been debated whether some late reactions to PPD are a result of active sensitization (23–25). In China, there is no current legal requirement for ingredient labelling on cosmetic products (26). With a booming economy and potential influence of western lifestyles, it is possible, and even probable, that millions of Chinese citizens will become exposed

to PPD in hair dyes in the near future. We urge close monitoring of trends in PPD patch test positivity in Asia generally. Furthermore, one should be aware that other hair dye ingredients are also capable of sensitizing upon exposure (27, 28).

Lower prevalence of PPD sensitization was identified in general population compared with patch test populations. As several large studies (35%) were performed with TRUE tests, this may underestimate true prevalence. The TRUE test may give false negative reactions to PPD when compared with test systems using allergens in Finn[®] chambers (29–31). Furthermore, some studies only performed D2 readings, which introduce the possibility of a substantial number of missed positive reactions (17, 21). Thus, population based studies did not allow us to estimate whether PPD sensitization has increased or decreased in recent decades.

When analyzing epidemiological data, one should be aware of potential pitfalls. Firstly, patch test populations should ideally be standardized to make exact comparisons. Despite the fact that the vast majority of patch test populations were not standardized, the age and sex distributions were, to a great extent, comparable, especially when data were stratified into different geographical regions. Thus, potential bias caused by the lack of standardization appears limited, and a comparison of patch test results in this study seems justified. Secondly, patch test readings should be performed using identical criteria. This is difficult to assess, but most studies reported that they used the criteria of the International Contact Dermatitis Research Group (32). Thirdly, comparable test systems and test concentrations should be utilized. Because standard patch test series were used in the majority of dermatitis patients, we estimate that the test systems and their results were broadly comparable. Finally, patient selection criteria should optimally be identical, which was clearly not the case with so many different health care systems involved.

The relevance of PPD reactions to the presenting complaint may be 44–47% (33) or 64% (34). Furthermore, a recent meta-analysis assessed that PPD ranked 9 of 24 TRUE test allergens in terms of relevance of positive reactions (35). Nevertheless, it is important to realize that reactions that are 'not relevant' are also of epidemiological importance. Indeed, as the prevalence of allergy increases in the general population, one would expect the number of reactions 'incidentally found' to increase, as observed with nickel allergy. In a population with a high frequency of sensitization, many are at risk of clinical reactions, which in the case of PPD sensitization may be severe.

Some authors have quoted exposures other than from hair dyeing as causes of PPD allergy. Many of these, e.g. fur dyes, printer's ink, photographic work, X-ray film fluids, and rubber vulcanization are mainly of historical interest. A more recent cause, temporary henna tattoos, only caused 2.6% of all PPD reactions in one recent report (15), although it is conceivable that this could be higher in other centres or in the future. Cross-reactions to other allergens in the baseline series are also quoted, such as with benzocaine and IPPD (N-isopropyl-N'-phenyl-paraphenylenediamine). However, these have recently been reported as being uncommon (10% and 3%, respectively) and with benzocaine, more related to the severity of the PPD reaction (36, 37). Azo dyes may also cross-react to PPD, and it has been assessed that 20–28.5% of patients sensitized to textile dyes also have positive reactions to PPD (38–41). Exposure to azo dyes from shoes may cause foot dermatitis and cross-sensitization to PPD (42). However, the primary cause of sensitization in dermatitis patients in general is most often with PPD, whereas primary sensitization to azo dyes is much less common (38, 41, 43). Cross-reactions with other aromatic amines such as *p*-toluenediamine (PTD) may also occur (44). However, as sensitization from both PPD and PTD predominantly comes from hair dye exposure, and the general advice to allergic patients is to avoid all aromatic amine hair dyes due to cross-reaction potential, the primary cause of sensitization is of limited importance, other than the realization that permitted concentrations of both agents should be regulated if prevalence of hair dye allergy is to be controlled. Finally, it is generally acknowledged that occupational cases only account for a minority of cases (36, 45). Taken together, the predominant cause of PPD allergy is consumer-related hair dye exposure (46–48). This was appreciated decades ago when Baer et al. speculated that the increasing prevalence of PPD sensitization between 1937 and 1962 was caused by frequent hair dyeing (49).

Conclusion

This review of published data demonstrates that the prevalence of PPD sensitization is high among dermatitis patients in Asia, Europe, and North America. Relevant positive PPD reactions are most often associated with hair dye exposure, although some positive reactions may be the result of cross-sensitization. Nevertheless, affected individuals are at risk of clinically severe reactions upon hair dyeing. Because hair dyeing is now a frequent cosmetic procedure in both men and

women, stronger regulation to reduce and/or eliminate exposures and enforcement of this are required urgently.

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