



Clinical and experimental aspects of allergic contact dermatitis to para-phenylenediamine

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Abstract The allergenicity of para-phenylenediamine (PPD) is related to oxidative processes on and in the skin. Patients with stronger reactions to PPD are significantly more likely to have a clear history of reacting to normal consumer hair dye. Those with stronger reactions are much less likely to be still dyeing their hair. Individuals allergic to PPD have a significant frequency of simultaneous sensitivity to chemically related clothing dyes. A 24-hour test application of hair dye, which has been proposed as a self-screen, does not reliably predict all individuals allergic to PPD. Duration studies have proven that exposures of 5 to 30 minutes, the period used for hair dyeing, are sufficient to elicit reactions. A significant rise in the frequency of PPD allergy was observed over 7 years among our patch test population. Active sensitization from standard PPD patch testing is not common. Immunologic findings relating to PPD can correctly predict that if hair dyes are commonly used there will be a significant prevalence of allergy to PPD among the normal adult population and that some clinical reactions will be severe. To protect the public from allergy to chemicals in consumer products, immunologic and epidemiologic data should both be used by regulatory authorities.

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Historical aspects of para-phenylenediamine as a hair-dyeing agent

Para-phenylenediamine (PPD) is an aromatic amine that polymerizes within the hair shaft in the presence of a coupler, causing a change in color of the hair. Oxidative dyeing of human hair has occurred for more than 100 years and arose from observations that the colorless compound PPD produced a colored compound when subjected to oxidation and that this could color a variety of compounds,

including hair. The first patent related to oxidation dyeing of human hair was applied for in 1883, using PPD or 2,5-diaminotoluene.¹ Soon after, hydrogen peroxide was used as an oxidizing agent in hair dyeing. Up to 1930, a further 79 hair dye chemicals were patented, mainly by German textile dye companies.

Concerns about allergic reactions were soon expressed. This led to restrictions and even banning of the public use of these chemicals in several European countries.² Oscar Wilde may well have been one of the first documented cases.³ He suffered from a persistent itchy eruption on his face and neck, which made him scratch constantly. On going to jail, his hair “became white within months” and on release, the color quickly returned.

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Allergic contact dermatitis to PPD and the cutaneous immune system

Haptenic properties of PPD

PPD belongs to the family of aromatic amines (Figure 1). Aromatic amines are closely related to catechols, such as urushiol, and hydroquinones.⁴ Mayer proposed the formation of p-benzoquinone in vivo as a possible explanation for the allergenicity and cross-reactivity of aromatic amines, including PPD.⁵ In clinical studies, 93% of individuals allergic to PPD had reactions to 2 or more hair dye-related chemicals.⁶ The molecular alterations of PPD required for its immunogenicity are not fully identified.⁷ Complex oxidation of PPD occurs when it is exposed to oxygen in the air for a prolonged period on the skin or in solution, the precise mechanisms of which are again not fully understood.⁸ A recently proposed “prehapten” concept suggests that autooxidation of PPD by air oxygen is pivotal for its immunogenicity.⁹ Several highly immunogenic autooxidation products, such as the trimer Bandrowski's base (BB; Figure 2) and the monomer, are known.^{10,11} The oxidation of a PPD derivative to the reactive benzoquinone diimine formed by air oxygen has been postulated as a prerequisite for its reactions with proteins.¹²

Once permeated through the epidermal barrier, skin metabolism studies reveal acetylation as the major deactivating metabolic pathway and epidermal keratinocytes as the responsible skin cells due to their high content of the mediating enzyme *N*-acetyltransferase 1.¹³ Acetylated PPD cannot stimulate T cells from PPD-allergic patients, suggesting that acetylation detoxifies PPD.^{13,14} On patch testing, only 1 of 16 of PPD-allergic patients were patch test-positive to the PPD acetylated compound *N,N*-diacetyl-para-phenylenediamine and none to mono-acetyl-PPD.¹⁵

Studies of oxidation of PPD have been conducted.⁸ After PPD was exposed to strong oxidizing conditions, a new monomer (probably benzoquinone), a dimer, and a trimer (probably BB) were identified by chromatography/mass spectrometry after 30 minutes. High levels of benzoquinone



**Small molecular weight
Avid protein binding**

Fig. 1 Para-phenylenediamine is characterized by small molecular weight and avid protein binding.

Bandrowski's base

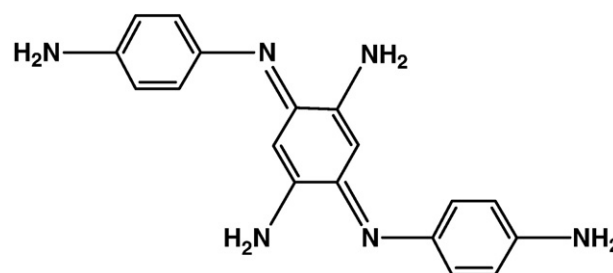


Fig. 2 Bandrowski's base.

are produced after 8 hours. BB was also produced after PPD was added to aqueous solution saturated by air oxygen, but at a much lower level. BB is also formed, when PPD is incubated with keratinocytes, suggesting that epidermal oxidation occurs.^{16,17}

When PPD is applied under oxidative hair dyeing conditions, production of nonreactive high-molecular-weight polymerized hair-coloring molecules should be chemically preferred due to the excess presence of couplers.^{8,18} When the formation of final coloring molecules is completed, up to 1.1% of unconsumed PPD is found.¹⁹ Unconsumed PPD that arrives in the living epidermis is considered predominantly to undergo acetylation (becoming nonallergenic), because most PPD-derived products reaching the plasma are diacetylated and more than 80% are mono- or diacetylated, when excreted in the urine.^{20,21} This is assumed to be due to the high capacity of keratinocytes to *N*-acetylate-PPD through activity of *N*-acetyltransferase 1.¹³ If, however, acetylation pathways become saturated, then oxidation of PPD could then occur. The equilibrium between enzymatic deactivation (acetylation) and activation (oxidation) of PPD is critical for obtaining an epidermal concentration of activated PPD that provides effective dendritic cell migration and activation to induce skin sensitization.⁸

Allergic contact dermatitis to PPD and innate immunity

As noted above, PPD and its oxidation products can activate dendritic cells in vitro. At noncytotoxic concentrations, PPD induces intercellular adhesion molecule expression on keratinocytes, production of hydrogen peroxide, and superoxide, a significant decrease in membrane polyunsaturated fatty acid and a transient increase of superoxide dismutase and catalase, both markers of the antioxidant system.^{22,23} Further in vitro work has shown that incubation with PPD (but not BB) causes induction of cyclooxygenase-1 and cyclooxygenase-2 enzymes in keratinocytes within 48 hours.²⁴ Cyclooxygenase activity induces prostaglandin formation; keratinocyte-derived prostaglandin E2 (PGE2) initiates immune responses by promoting migration and maturation of Langerhans cells, and PGE2 is involved in T-cell activation.^{25,26} These findings are

consistent with PPD delivering a “danger” signal to initiate cutaneous immune activation.

One of the proposed mediators of danger signals and a cytokine involved in initiating innate immunity in allergic contact dermatitis (ACD) is tumor necrosis factor (TNF)- α . The genetically programmed amount of TNF- α released in response to stimuli depends on promoter regions, some of which have well-established genetic polymorphisms. The best described of these is at TNF-308. We previously described the adenosine (A) at position 308 as being associated with susceptibility to cutaneous irritancy, and others have described an association with multiple contact allergies.^{27,28} A case-control study evaluated the distribution of variations in the regulatory region of the gene for TNF- α (*TNF 308 G/A*) in 181 white individuals with a history of ACD and sensitization to PPD and 161 individuals with no history of sensitization to PPD.²⁹ The frequency of *GA* or *AA* TNF- α genotypes was significantly higher in individuals sensitized to PPD than in age-matched and gender-matched controls ($P = .0016$). Previous studies indicate that the adenine nucleotide at position 308 of the promoter region of the TNF- α gene is associated with increased production of TNF- α .^{30,31} TNF- α is an essential cytokine in dendritic cell maturation and migration to lymph nodes and is also a key proinflammatory cytokine and promoter of the release of other cytokines within the affected skin.³²

Allergic contact dermatitis to PPD and the primary adaptive response: Potency

Potency of PPD was analyzed in the Localised Lymph Node Assay (LLNA) in two centers.³³ Proliferative responses to PPD were measured at five concentrations (0.05%, 0.1%, 0.25%, 0.5% and 1%), together with vehicle-treated (acetone: olive oil) control. In every experiment, PPD provoked a vigorous proliferative response; above 0.25% the observed levels of lymph node cell proliferation were very similar between laboratories. The derived EC3 values showed a very high level of consistency between 0.06% and 0.20%, making it an extremely potent (class 1) allergen.

Our data show that the oxidation product of PPD, the trimer BB, is more potent than PPD, with an approximately 10-fold difference in EC3 values between BB and PPD.^{8,34} These aromatic amines are more potent than dinitrochlorobenzene, and the only equivalent contact allergens in terms of potency are diphenylcyclopropenone and (chloro)methylisothiazolinone.³³ This is consistent with historical experimental human sensitization studies which may not be repeated on ethical grounds.

BB, oxidized PPD, and PPD were compared for their *in vitro* ability to activate dendritic cells, as adjudged by induction of CD86 surface marker and up-regulation of interleukin (IL)-1 β and IL-8 genes.⁸ BB was the most potent inducer of CD86, oxidized PPD was less potent, and fresh PPD was much weaker. Similar patterns were seen with

regard to cytokine gene up-regulation. Other authors have also found similar results, with BB being the most potent activator of dendritic cells.³⁵ Activation of dendritic cells *in vivo* may, therefore, not be due to PPD but to its oxidation products. The changes noted in dendritic cell activation are associated with migration to the local lymph node.

In a recent study using T-cell clones from PPD-allergic individuals, PPD stimulation of T cells could be produced in different ways; with presentation dependent on protein complex formation (42/48 clones), with processing by APCs (32/68), or by direct triggering without complexing or processing (12%). Cysteine was identified as the site for PPD binding to albumen to stimulate T cells.³⁶

Allergic contact dermatitis to PPD and the secondary adaptive immunity: Elicitation studies

Very low concentrations (0.01%) of PPD can elicit reactions in some individuals. In addition, as little as 15 minutes can be an adequate exposure in some individuals to elicit a delayed-type hypersensitivity reaction. A relationship exists between time and dose in producing elicitation reactions to PPD and wide interindividual variability.³⁷⁻⁴⁰ Applications of 1 or 2 minutes, however, do not give a reaction regardless of the concentration used (up to 1%); thus, we found a minimum time of application of 5 minutes is required to elicit a reaction. Air auto-oxidation of PPD occurs only from 5 minutes exposure onwards, suggesting that auto-oxidation of PPD is required for patch test elicitation.⁸ Repeated open application of 5 minutes daily demonstrates a cumulative effect: 8 days of repeated 5-minute applications more than doubles the number of positive elicitation reactions compared with one 5-minute application. The allergen would appear to accumulate in the skin. Secondly, the tissue priming effect of chemical perturbation results in locally enhanced immune surveillance, facilitating elicitation response to allergens at lower dose concentrations.^{41,42}

We found an exact correlation with the cumulative time needed for repeat exposures to elicit a reaction and the time needed for a reaction to the single exposure.³⁹ Rat skin exposed to radiolabelled PPD showed that cumulative exposure time and single exposure time correlated with retention of radiolabelled substance within the skin. In addition, a positive correlation was found between the grade of the original patch test reaction and the appearance and intensity of the time/dosed elicitation reaction. In comparing the use of hair dye preparations applied for 24 hours with 48-hour patch testing, there was good correlation with the more sensitized patients (2+ or 3+); however there was poor correlation with those who are only modestly allergic to PPD (1+).⁴⁰ As a result, self-tests using commercial hair dye material may only be reliable for those with strong hypersensitivity to PPD.

A Danish group found 7% and 13% of PPD-allergic patients reacted to 48 hours of 0.005% and 0.01% PPD concentrations, respectively, which is consistent with our data for minimum concentration for elicitation.⁴³ There were also no differences in elicitation thresholds for different regional areas of the skin (upper back, retroauricular area, and lateral aspect of upper arm).

Another study found that individuals who had been sensitized to a fixed amount of dinitrochlorobenzene, who failed to respond to a first eliciting dose, often gave a response on a second elicitation challenge to the same dose.⁴⁴ Repeated elicitation doses can, therefore, be additive and augment the elicitation response. Repeated applications that can elicit a response when a single application fails is the basis for the repeat open application test, which is used to demonstrate an elicitation reaction by applying a substance to the same area of skin daily for 7 to 14 days. For patch testing with methyldibromo glutaronitrile, 0.15% petroleum is used; however, when used at as low a concentration as 0.005% in a repeat open application test, as many as 33% of sensitized individuals gave a positive reaction.⁴⁵

Thus, our data are in keeping with other published data: Repeat applications will elicit a positive reaction with a significantly lower concentration per application—this is of importance in regard to determining safe levels of chemicals in consumer products, such as preservatives, fragrances, and hair dye chemicals, which are also potential allergens. Incremental exposures and increased exposure time all add to the total dose, and it is this total dose that appears to be the crucial factor regarding the degree of response.

Finally, some evidence suggests that the presence of other contact allergens may enhance the sensitizing capacity of PPD. A study using the mouse local lymph node assay found evidence that PPD combined with the preservative contact allergen methyldibromo glutaronitrile had a synergistic effect on sensitizing capacity that was more than merely additive.⁴⁶

Other aspects of allergic contact dermatitis to PPD and secondary adaptive immunity

An investigation was conducted of *in vitro* T-cell reactions in 13 individuals who showed at least 2+ responses in patch test reactions.⁴⁷ Patients with 3+ patch test reactions had significantly stronger *in vitro* peripheral blood mononuclear leucocyte proliferation response to PPD than patients with 2+ patch test reactions. Restricted T-cell receptor usage was observed in some individuals. A detailed analysis of 34 T-cell clones showed broad cross-reactivity (64.7%) between PPD, *p*-toluenediamine, BB, and *p*-aminazobenzene, all aromatic amines. A subgroup of 18 T-cell clones were analyzed by flow cytometry. The tested clones were CD-4+ and T-cell antigen receptor (TCR)- $\alpha\beta$ except one clone, which was

CD8+ and expressed TCR- $\gamma\delta$. Interestingly, transfer of contact hypersensitivity to PPD in mice by $\alpha\beta$ T cells is assisted by the presence of PPD-responsive $\gamma\delta$ T cells.⁴⁸ Another study also found that cells responding to PPD were CD4+.¹⁷

Stimulation of T cells with PPD and BB resulted in secretion of IL-4, IL-5, IL-13, TNF- α , macrophage inflammatory protein-1 α and -1 β (both CCR5 ligands), and RANTES (regulated upon activation normal T-cell expressed and secreted).^{17,49} Th2 cytokines appear to be produced by lymphocytes presumably involved in ACD and may possibly represent a regulatory component. High levels of IL-4 and the related IL-13 have been detected in skin biopsy specimens of delayed type-hypersensitivity reactions.^{50,51}

ACD to PPD and patch testing

We have demonstrated that among patients attending our cutaneous allergy clinic in London, there is a wide range of elicitation reactions to PPD on patch testing.⁵² Patients with stronger patch test responses are more likely to have a history of reacting to hair dye and less likely to continue dyeing their hair. Therefore, against classical teaching in contact dermatitis, strength of patch testing can have clinical implications. This study also demonstrated the determination of many of the patients with a recorded history to continue dyeing their hair, even when they have been advised to stop and warned that they may develop allergic reactions after using dyes in the future.

We found a female/male sex ratio of 2:1 amongst PPD-allergic patients, which is in keeping with other European centers.⁵³ This is in contrast to several Asian and Middle Eastern centers where most patients are men.⁵⁴⁻⁵⁶ Of our patients with Southern Asian surnames, we found a similar pattern of men outnumbering women. This is perhaps best explained by both a relatively greater frequency of hair dyeing amongst Asian men and a greater frequency of dyeing facial hair. Facial hair is often dyed once a week, whereas scalp hair is dyed every 1 to 6 months, and frequency of repeated application of allergen appears to be a critical factor in determining sensitisation.⁴²

In the 1995-2004 survey, 9% of our study group were hairdressers, compared with 29% in the previous survey (1986-1992).⁵⁷ This is at variance with a recent statement that hairdressers now comprise most PPD allergy cases.⁵⁸ Hairdressers were not more likely to have 2+ or 3+ reactions.

There was a high incidence of concomitant reactions to various groups of allergens not chemically related, such as nickel and rubber. Evidence indicates TNF- α polymorphisms are a genetic marker for individuals to have multiple contact allergens, and that even more recently, TNF- α polymorphisms have been linked to PPD allergy.⁵⁹

Ten percent of PPD-allergic individuals reacted to "caine" mix, which contains the potentially cross-reacting agent

benzocaine. The likelihood of reacting to “caine” mix increased linearly with the strength of a positive PPD patch test reaction, suggesting a simple cross-sensitivity. Reactions to N-isopropyl-N-phenyl-PPD (black rubber) and para-amino-benzoic acid (sunscreen) were observed much less commonly (both 3%), and there was no linear relationship with strength of PPD reactivity, suggesting that the mechanism of simultaneous patch test reactivity is more complicated than simple allergenic cross-reactivity. The frequency of reactions to these PPD-allergic patients is, therefore, far less common than “common knowledge” has assumed. Only a small minority of such patients need to avoid these agents.

In another study, we found that Disperse Orange 3 was the commonest azo dye coexisting allergen in PPD-allergic individuals (46%).⁶⁰ Also, reactivity increased with azo dyes in general within the group showing stronger PPD reactions (2+, 3+). The high frequency of reactions to Disperse Orange 3 has been described before. Cosensitization to PPD was present in 66% of individuals sensitized to Disperse Orange 3,⁶¹ most of whom had a clear history of reacting to hair dyes. The authors suggested primary sensitization in these individuals could be acquired from hair dyes and may represent cross-sensitivity. Disperse Orange, however, can be degraded to PPD and nitroaniline within the skin,⁶² so a simultaneous patch test reaction to a Disperse Orange 3 patch test is perhaps not surprising, because it may represent local production of PPD within that test site.

Other dyes commonly reacting in PPD-allergic patients also have simple structures with a single azo bond and may be metabolized to yield PPD. The dyes with more complicated structures and multiple azo groups may be less amenable to cross-reactivity or metabolism to PPD. The possibility of concomitant allergy to clothing dyes remains a problem. Unlike toiletries, there is no compulsion with the European Union to label constituents of clothing. Our own experience is that clothing dye dermatitis remains an uncommon problem, even within patients who have severe hair dye allergy. One should, however, be alert for a sudden increase in the incidence of clothing allergy.⁶³

Complications from patch testing to PPD

Severe elicitation reactions

These can be very uncomfortable and sore: 3+ reactions can take several days or even weeks to resolve. Severe reactions in PPD allergy have particularly been seen in patients who have been sensitized through exposure to high doses of PPD contained in black henna tattoos and who have then been patch tested to the standard 1% petroleum PPD concentration.⁶⁴

Vacationers at holiday resorts may get temporary black henna tattoos. Pure natural henna (*Lawsonia inermis*) has

very low allergenic potential but is often adulterated with high concentrations of PPD to enhance the coloring. Concentrations of PPD have been measured as high as 15.7% compared with the allowable limit of 3% in hair dyes.⁶⁵ Human studies have previously shown how highly sensitizing PPD is when applied at concentrations of 10% or more.⁶⁶ In our review of PPD allergic patients, 2.5% of the study total had had received a temporary black henna tattoo in the past.⁵² Three developed a 2+ reaction and seven developed a 3+ reaction. To prevent such frequent severe reactions, which can be uncomfortable for the patients, we have, therefore, demonstrated that 0.01% is usually sufficient to elicit a reaction, without severe 3+ reactions.⁶⁴ Exposure to high concentrations of PPD, as in a black henna tattoo, and prolonged exposure on skin without hair will lead to production of high levels of auto-oxidized products and strong allergic reactions.⁸

Active sensitization

Active sensitization to PPD was reported with a late irrelevant reaction at 15 days.⁶⁷ Patch testing to 1% PPD is considered to carry a high risk of active sensitization.⁶⁸ Reactions later than 3 days were considered as being clinically irrelevant and, therefore, possible active sensitization events; however, this has been disputed because many genuine elicitation reactions occur even after 7 days.⁶⁹

If active sensitization to PPD from patch testing is a common occurrence, then we should expect a higher rate of positive patch test reactions to PPD on repeat patch testing (ie, after the individual has already been exposed to PPD under patch test conditions before). Our study showed no significant increase in PPD-positive patch test reactions in individuals receiving repeat patch tests compared with those who only had single patch tests.⁷⁰ Our findings indicate that active PPD sensitization from patch testing is uncommon, and this observation is corroborated by results from the Bangkok-hair dye study. Part of this study monitored 600 PPD patch test-negative patients for 6 months after they were instructed not to dye their hair during this time. They were used as a control for another group who were dyeing their hair over 6 months to see how many would become sensitized to PPD during this time. Two in this negative control group were patch test-positive to PPD on repeat testing after 6 months. One volunteer had evidently been dyeing her hair; therefore, only 1 in 600 may have been actively sensitized by patch testing, the alternative being that the first reading was a false-negative result.

Epidemiologic aspects of ACD to PPD in patch test clinics and the general population

For more than 100 years, PPD and other related members of the aromatic amine family have been the main agents

used in permanent hair dyes, and more than two-thirds of hair dyes currently contain PPD. Its low-molecular-weight ability to penetrate skin structures, its strong protein-binding capacity, and its rapid polymerization in the presence of a coupler and oxidizing agent make it an effective dyeing agent. These properties, however, also make it an effective and potent contact allergen. No satisfactory alternative to the aromatic amine agents is available for use in permanent hair dyes.

As previously mentioned, contact allergy to PPD and related aromatic amine dyes is detected by patch testing using 1% PPD in petrolatum. This is included in the baseline series of patch tests used to screen for contact allergy in patients with dermatitis. Such screening, however, may fail to detect allergic reactions to other hair dyes.⁷¹ There was a steady state of between 2% and 4% of our patch test population allergic to PPD during the 1980s and 1990s in our London clinic.⁷² After 1999, however, there was a significant rise over 6 years to 7.1% by 2006, in the same clinic.⁷³ This rise could not be attributed alone to an increase in occupational exposure, medicolegal claims, the use of temporary black henna tattoos containing high concentrations of PPD (often when on beach holidays), or a greater proportion of South Asian patients, who tend to have higher rates of allergy to hair dye.⁵⁶

Screening of 2545 normal adult volunteers in Bangkok by patch testing showed a 2.7% prevalence of PPD allergy, which, when extrapolated to the general population, suggests more than 1 million Thai adults may be sensitive to PPD. In Germany, up to 1.3 million adults in the general population may be sensitive.³⁹

Market research indicates that more people are dyeing their hair and are doing so at a younger age. A 1992 survey of young people in Tokyo found that 13% of girls in high school, and 6% of women and 2% of men in their 20s reported using hair colorants.⁷⁴ By 2001, the proportions using hair coloring agents had increased in these groups to 41%, 85%, and 33% respectively; furthermore, girls in high school and young women were dyeing their hair at more frequent intervals. Hair dye sales for one leading Japanese company more than doubled, and shipments of hair dye to Japan doubled in the 10 years to 2001. In Denmark, 75% of women and 18% of men have used hair dye, and the median age for first use of hair dye for both men and women is during the teenaged years.⁷⁵ Severe hair dye allergy has recently been reported among children.⁴³

Published data on allergy to PPD, with reports from both eczema patients (ie, from patch test clinics) and healthy populations, was recently reviewed.² Data from Europe, Asia, and North America were studied, but studies from South America, Africa, and Australia were excluded because relatively few were identified from these areas. PPD concentrations using 1% PPD in petrolatum were used for analysis; other studies using higher or lower concentrations were used for weighted

average prevalence. All studies used the International Contact Dermatitis Research Group criteria for assessing positive patch test reactions.

The median prevalence of PPD allergy 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. Analysis of aggregated studies shows an increase in prevalence of PPD allergy among Asian dermatitis patients since 1984. In Europe, there has been a plateau of prevalence to PPD allergy of between 2% and 6% since the 1980s. North America shows a consistently higher prevalence of PPD allergy compared with Europe, with most studies reporting a prevalence of between 4% and 7%. Although no definitive reason is known for this high prevalence in North America, the authors speculated that it might be a result of large African American and Hispanic American populations, who tend to opt for darker shades than Northern Europeans. Besides the London study, however, individual patch test centers in Sweden, Denmark, and Germany have recently demonstrated an increasing prevalence of allergy to PPD.^{2,73,76,77}

All studies on healthy populations were reported from within Europe except for the Thai study.³⁹ Studies in Europe showed lower prevalence of PPD allergy in healthy populations of 0% to 1.6% compared with 2.7% in the Thai study. In general, studies from Scandinavia amongst healthy populations showed a lower prevalence than reported from elsewhere, and this may be due to lighter shades of dye generally used, which would contain significantly lower concentrations of PPD.

PPD allergy was quoted to be clinically relevant to the presenting complaint in 44% to 47% of cases⁶⁸ and in another study in 64% of cases.⁷⁸ The sizable number of cases where the PPD allergy was adjudged not to be relevant has been given as a cause for omitting PPD in testing; however, if "not relevant" reactions are becoming increasingly observed, this could indicate that PPD allergy is becoming commoner in the population at large (ie, as with the high numbers of "nonrelevant" positive patch test reactions to nickel) and that more individuals presenting with dermatitis not caused by hair dye allergy will still be coincidentally allergic to hair dye.

There have also been suggestions that consumer use of PPD is only one of many causes of PPD allergy. Many of the quoted sources of exposure, including fur dyes, printers ink, photographic work, X-ray films, are only of historical interest. Henna tattoos only accounted for 10% of the increased prevalence reported in London,⁵² although this could conceivably rise with time because the practice of vacationers getting temporary henna tattoos while on holiday is common, even in children, who may then go on to start dyeing their own hair or become hairdressers several years later. The cross-reactions with azo dyes are more likely to be driven by PPD allergy than azo dye allergy.⁶⁰ Occupational cases (hairdressers)

constitute only a minority of reported PPD-allergic individuals in most studies.^{52,79} Consumer use of PPD in commercial hair dye products appears to be the main cause of allergy in these studies.

It is possible to extrapolate contact allergy in the general population to different agents from data derived from contact dermatitis clinics.⁸⁰ For PPD allergy, prevalence rates derived from clinics are estimated as between 2.1 and 3.2 times higher than in the general population. Even this may be conservative; in the Bangkok study, which was considerably larger than other screening studies of healthy populations, 2.7% of the adult population was patch test-positive compared with 4.6% in a Bangkok clinic (ratio of 1.7).⁸¹ Although prevalence rates of allergy from dermatitis (patch test clinic) populations has, therefore, some association with the prevalence among the general population,⁸⁰ there is still a paucity of studies determining the prevalence of ACD to chemicals in consumer products among the general population and more are needed. The Bangkok study suggests a high prevalence of contact allergy to PPD and the need for reappraisal of the use of contact allergens in consumer products. Current epidemiologic data suggest that ACD to hair dye has reached hyperendemic levels on most continents. Regulators will need to devise a means of assessing the prevalence of allergy to consumer product-related chemicals within the general population and when intervention is required.

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