Symposium - Contact Dermatitis

Contact dermatitis to hair dye: An update

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ABSTRACT

Exposure to hair dyes has long been known as a significant risk factor for development of allergic contact dermatitis among the exposed population as these lead to severe eczema of face and upper trunk in the consumer and hand eczema in hair-dressers. Currently, para-phenylenediamine (PPD) is the main ingredient used in permanent hair color products in the market and is the most important allergen. Prevalence of PPD sensitization is high in patients with contact dermatitis across all continents, with hair dye use being the commonest cause. In order to decrease the burden of disease, use of alternative natural dyeing agents among consumers and use of barrier neoprene gloves among hairdressers should be encouraged apart from stringent legislation to reduce the amount of PPD reaching the consumer.

Key words: Allergic contact dermatitis, Bandrowski's base, para-phenylenediamine

INTRODUCTION

Dyes can be defined as colorants that are soluble in the water and/or an organic solvent, have a particle size of less than 0.01 μm, and color substrates to which they have affinity.[1] They have found widespread usage in industry as well as in many daily use products. These are used as antioxidants and as intermediates in chemical synthesis of pesticides, pharmaceuticals, explosives, rubber etc. Hair dyes, belonging to the broad group of arylamines, are one of the most frequently used hair cosmetics. They are used not only to hide graying hair but also to change one's hair color to enhance beauty. In fact, "Eighteen books of the secrets of art and nature"; a book published in 1661, described various methods of coloring hair black, gold, green, red, and even white.[2]

Hair dyeing with henna became increasingly popular during the 19th century, but was gradually replaced by p-phenylenediamine (PPD) as the preferred hair dye in Europe.[3] PPD was first described in 1863 by the German chemist Hofmann.[4] Due to the fear of allergic contact dermatitis due to PPD in hair dyes, its public use was banned in Germany in 1906 and later in several other European countries.[5] It is speculated that Oscar Wilde may well have been one of the first documented cases of allergic contact dermatitis to hair dyes.[6] In the 1930's, Bonnevie suggested that PPD should be included in patch test standard series.[7] Today, hair dyes are regulated in the European Union (EU) Cosmetic Directive such that PPD is allowed in a concentration of up to 6% and toluene-2,5-diamine up to 10%.[8]

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CLASSIFICATION OF HAIR DYES

Based on their chemical composition, hair dyes can be broadly classified into 3 main categories – vegetable dyes, metallic dyes, and synthetic organic dyes [Table 1].

1. Vegetable dyes: Henna is obtained from the dried leaves and stem of *Lawsonia intermis* which grows in Egypt, Tunisia, and India. Henna is the only available vegetable hair dye. Natural henna takes several hours to be absorbed into the skin and imparts a brownish-orange color. Its active principle is lawsone (2-hydroxy-1,4-

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Table 1: Classification of hair dyes

A.	Vegetable hair dyes
B.	Metallic hair dyes
C.	Synthetic hair dyes
	a. Direct hair dyes
	b. Oxidation hair dyes

naphthoquinone). In recent years, temporary henna tattoos have become fashionable among children and youth. Black henna refers to the mixture of natural henna to which PPD is added in order to decrease application time and intensify the color. In addition, natural substances such as lemon oil, vinegar, and eucalyptus oil may be added to obtain different shades.

By itself, henna has a low allergic potential, and most cases of allergic reactions attributed to henna are actually due to the additives that are added to henna mixtures such as diaminotoluenes and diaminobenzenes.[9] PPD is responsible for most of the complications reported after henna tattoos: Localized or generalized contact dermatitis, hypertrophic or keloid scars, and pigmentary changes. Kazandjieva reported 31 cases of allergic contact dermatitis due to temporary henna tattoos.[10] Rarely, allergic contact dermatitis to pure henna has also been reported.[11]

2. Metallic dyes usually contain lead acetate and salts of bismuth, silver, copper, nickel, and cobalt, and they may be used to give a range of colors. These tend to make hair brittle and impair subsequent permanent waving and are used infrequently.
3. Synthetic organic dyes are of 2 types – direct and oxidative.[12]
   a. Direct hair dyes include the temporary and the semi-permanent hair dyes.
      i. Temporary dyes (color rinses) coat the hair and are removed by shampooing. Examples include the anthraquinone colors, azo dyes, eosin YS dyes etc. The colorants in temporary hair color are large, do not penetrate the cuticle layer and remain adsorbed to the hair shaft, and hence are easily removed. If the hair is excessively dry or damaged, it may allow for migration of the pigment to the interior of the hair shaft and thus a longer stay.
      ii. Semi-permanent dyes are low molecular weight chemicals, which can penetrate the hair shaft and are retained for about 5–10 hair washings only. They are colored-compounds and do not require any oxidation for their coloring action. The final color of each strand of hair depends on its original color and porosity, giving a more natural look with subtle variations compared to the permanent dye. These include nitrophenylenediamines, nitroaminophenol, and anthraquinones. Semi-permanent dyes contain no, or very low levels of developer, peroxide or ammonia and are, therefore, safe for damaged or fragile hair.
   b. Oxidative or permanent dyes form the most important group of hair dyes and are most frequently incriminated in causing allergic contact dermatitis. They disguise grey hair and change the original color of hair through a range of brown to black shades.

Semi-permanent hair color refers to a permanent hair color that contains an alkaline agent other than ammonia (e.g., ethanolamine, sodium carbonate) with a much lower concentration of hydrogen peroxide than that used with a permanent hair color. They can't color hair to a lighter shade than it was before dyeing as the alkaline agents employed are less effective in removing the natural pigment of hair than ammonia and are less damaging to hair than their permanent counterpart.

Recently, a new semi-permanent hair color has been introduced in the market (Vegetal biocolor), which claims to be free of the allergic adverse effects of PPD-based colors. The product is based on combination of various natural dyes like henna, manjistha, catechu, coffee, and indigo. The long term follow-up of such products regarding their effectiveness in coloring the hair and potential adverse effects is still awaited.

CHEMICAL COMPOSITION OF HAIR DYES

Oxidative hair dyes are the most important group accounting for more than three-fourth of the market share. These involve mixing of 2 components – precursor along with coupler; and oxidizing agent, which leads to generation of the resultant hair dye on the hair. The precursors most commonly used belong to the group of arylamines and include para-phenylenediamine, para-toluenediamine (PTD), ortho-aminophenol, and para-aminophenol. The European Union (EU) inventory of ingredients employed in cosmetic products contains approximately 300 hair

dyes and colorants. The primary intermediates or precursors have little color of their own and are oxidized (possibly within hair shaft) by hydrogen peroxide to form colorless quinone-diimines. The polymerized intermediate now in the presence of a coupler reacts to produce dyes; large, colored molecules held within the hair shaft and are difficult to remove. Hair remains permanently colored. The couplers are meta-substituted derivatives of aniline. Based on the color that they produce, couplers are divided in 3 major classes:

i. Blue couplers include 1,3-diaminobenzene and its derivatives.
ii. Red couplers include phenols and naphthols, such as 3-aminophenol (CAS#591-27-5), 5-amino-2-methylphenol (CAS#2835-95-2), and 1-naphthol (CAS#90-15-3).
iii. Yellow-green couplers include resorcinol, 4-chlororesorcinol, and benzodioxoles.[13]

PPD (1,4-phenylenediamine; CAS 106-50-3, Figure 1a and b) is a colorless intermediate chemical in the production of dyes and antioxidants.[14] Production of a colored compound by PPD is a 3 step process. Firstly, there is oxidation of PPD to quinonediimine (C6H4NH2), which exists in equilibrium with the monoprotonated form. In the second step, this monoprotonated form attacks the coupler leading to electrophilic aromatic substitution. The last step involves the oxidation of the product of previous reaction to form the final dye, which binds to the hair because of its much larger size. Ammonia promotes bonding of dye with the hair. In the absence of a coupler, PPD oxidizes to form Bandrowski's base, a trimer, which has been shown to be a potent mutagen.[15,16] According to the prehapten concept proposed by Lepoittevin, autoxidation of PPD by air oxygen, which can occur as early as 5 minutes after application, is pivotal for its immunogenicity.[17] However, the combinations of precursors and couplers mainly produce dimers and trimers as reaction products with minimal or no Bandrowski's base.[18] In addition, 4-aminobiphenyl (4-ABP), a known carcinogen, may be present as a contaminant in hair dyes and was detected in 8 of 11 commercial hair dyes investigated with levels as high as up to 500 ppb.[19]

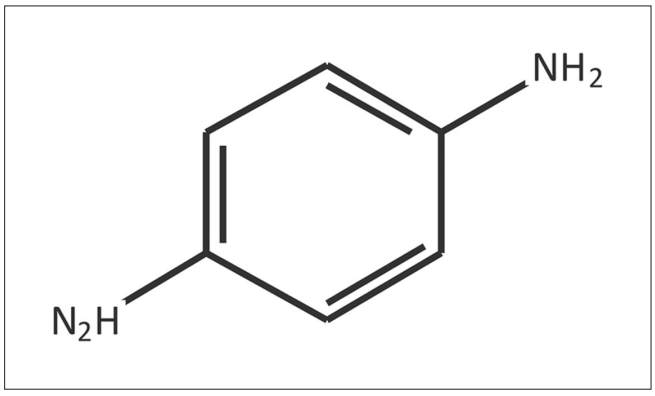

Figure 1a: Para-phenylenediamine

EPIDEMIOLOGY OF ALLERGIC CONTACT DERMATITIS TO HAIR DYES

PPD has been recognized as an important contact allergen for a long time, which can present with acute, subacute, and chronic dermatitis. Various studies have found the median prevalence of PPD positivity among dermatitis patients to be 4.3% in Asia, 4% in Europe, and 6.2% in North America; although there may be wide inter-country and intra-country variations.[5,20-22] Europe experienced a decrease in prevalence of PPD sensitization in the 1970s followed by steady, high prevalence ranging between 2% and 6%. The prevalence has remained high in North America. In Asia, the sensitization prevalence to PPD has ranged between 2% and 12% with relatively higher prevalence in Asian men than in women. This could be explained partly due to lack of adherence to the manufacturer's instructions by the consumer leading to application of a more concentrated final product. In addition, various cultural practices may account for these differences including dyeing grey facial hair and use of darker shades of hair dye. Since facial hair needs to be dyed more often than scalp hair, the frequency of contact to the allergen is increased and thus the risk of sensitization. We have also observed nearly fourfold

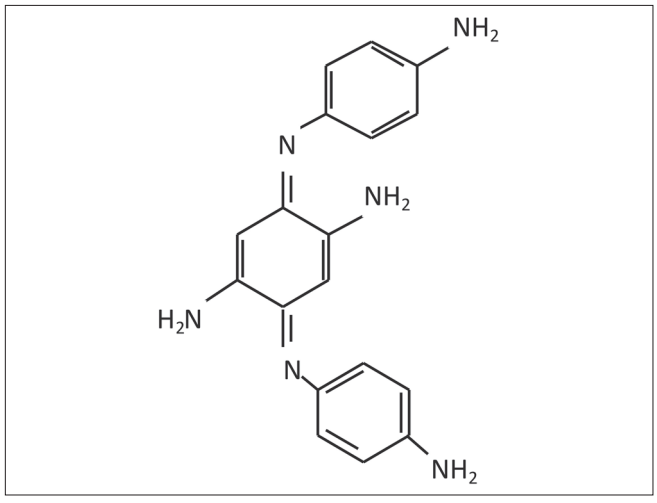

Figure 1b: Bandrowski's base

rise in PPD prevalence over the last decade over the last decade at our institute.[23]

Recently, there has been an increasing frequency of sensitization to PPD, which may reflect an increasing trend of allergies to hair dyes.[24] This has been accompanied by a significant increase in allergic reactions to para-tolulenediamine (PTD).[25,26] However, in view of the multitude of potential exposures to PPD and related compounds, few authors have questioned the role of hair dyeing in increasing the prevalence of PPD sensitization.[27] Schnuch *et al,* classified the patients showing patch test positivity to PPD into 3 groups – first was those with exposure to hair dyes, which included the hair dressers and the consumers (21.5%); second group included those with occupational exposure to leather and textile industry (35%); and the third was unspecified group (43.5%).[14] The patients in the first group had much stronger positive patch test reactions compared to other groups and had a significantly higher PTD positivity in addition to PPD. The second group apart from having a higher PTD positivity rates also showed positivity to other allergens like potassium dichromate, thiuram mix etc. Many patients in the unspecified group gave history of hair dye use in the past, and it is difficult to refute or confirm its role in PPD sensitization.

Allergic contact dermatitis to hair dyes in hair dressers – A special subgroup

Working as a hairdresser is associated with an increased risk of contact allergy. Uter *et al,* found contact allergy to glyceryl monothioglycolate (GMTG) to be the commonest in patients currently or previously working as hair dressers.[25] A steady decline in sensitization to PPD from 27.6% to 17.2% was observed during the period 1995 - 2002. A similar analysis during the period 2003 - 2006 showed ammonium persulfate (21.7%) to be the most common sensitizer followed by PTD (19.6%), PPD (18.1%), and GMTG (7.5%).[26] In a review by Khumalo *et al*,[28] prevalence of contact dermatitis was seen in up to 80% of hair dressers in smaller studies and 16.4% in larger studies. The most common presentation was that of hand dermatitis; acne keloidalis nuchae was seen in 1.3% - 13.7% of patients and tractional alopecia in 1% of subjects.[28] Hand dermatitis in hairdressers is not only due to the sensitizing and irritant capacities of some hair-cosmetic ingredients but also due to unsafe packaging, absence of protection with adequate gloves, and ignorance of safe handling of these chemicals.

PATHOGENESIS OF ALLERGIC CONTACT DERMATITIS TO HAIR DYES

PPD-containing hair dyes would be expected to elicit allergic reactions in sensitized individuals. Yet, doubts have been raised regarding its sensitization potential as it has been claimed that in-use hair dyes contain a large quantity of couplers that bind free PPD and thereby inhibit the sensitization potential of the product. Further, the mixture of color gel and developer (oxidant) results in rapid polymerization of the hair dye chemicals, which is washed within 30 min of application, thus having a minimal exposure time. Aeby *et al,* used a dendritic cell (DC) activation assay *in vitro* and the local lymph node assay (LLNA) *in vivo* to assess sensitizing potential of PPD containing hair dyes. It was observed that relevant DC activation was induced by oxidized product of PPD but not by PPD itself and its acetylated products. Both PPD and its oxidized product induced a positive LLNA test but not the acetylated product. Formation of Bandrowski's base was identified along with other di- and trimeric compounds, indicating the immunogenic potential of PPD oxidation products.[29]

Efforts have been made to estimate an exposure to precursors and couplers of oxidative hair dyes during and after hair dyeing. For this purpose, the concentration of unconsumed precursors after color development have been measured, and up to 1.1 % of PPD has been found after color development.[30] The Scientific Committee on Consumer Products (SCCP) has critically evaluated 11 combinations of precursors and couplers of oxidative hair dyes available on European market and determined the amounts of unreacted precursors and couplers in various formulations. Up to 12% - 84% of unreacted precursors and couplers in various experiments were present after 30 min of hair dyeing.[31] Skin absorption data including percutaneous absorption studies found the values to be between 0.04 and 15.2 $\mu g/cm^2$ for direct dyes; whereas, for oxidative hair dye, amines values ranging from 0.25 to 63.68 $\mu g/cm^2$ were measured.[32] Assuming a scalp area of 580 cm^2 and a body weight of 60 kg, these values correspond to internal doses of 0.4 to 616 $\mu g/kg$ body weight.[33] It can be concluded that in spite of presence of couplers and oxidizing agents, significant amount of unreacted precursors are available on skin surface and in the dermis to act as allergen.

The second issue is regarding the sensitizing potential of these agents. Bonefeld *et al,* evaluated the immunogenic potential of consumer available

permanent hair dyes in an animal model using a modified LLNA.[34] It was observed that the application of the color gel both alone and mixed with the developer induced skin production of interleukin (IL)-1β, tumor necrosis factor-α, and IL-6 as well as infiltration and proliferation of T-cells within the draining lymph nodes; with the inflammation being at least 20% more severe with the mixture. Reducing the exposure time to the hair dye reduced the skin inflammation and cytokine production. Further, it was noted that the inflammatory response was at least 50% higher when hair dye was washed away according to the manufacturer's protocol compared with mice exposed to 1% PPD that was not washed away. Thus, the chemical composition within final mixtures is a more potent immune activator than 1% pure PPD. These findings are in contrast to those by Aeby *et al*.[29]

Zhang *et al,*[35] conducted a population-based case-control study to assess whether the relation between hair dye use and risk of lymphomas is influenced by genetic variation in xenobiotic metabolic pathway genes. They observed a higher association of follicular lymphoma in females who started using hair dye before 1980's and were for carriers of certain genotypes.[35] Mortan *et al,*[36] also found similar results and correlated the risk of non-Hodgkin lymphomas with genetic variation in N acetyltransferase 1 (*NAT1*) and 2 (*NAT2*), which encode enzymes that metabolize aromatic amine compounds found in hair dyes.[36] Further larger studies are required to confirm the role of genetic variation in xenobiotic metabolism in the carcinogenicity of hair dye use.

CLINICAL FEATURES

Clinically, it may present as irritant contact dermatitis, allergic contact dermatitis, photocontact dermatitis, contact urticaria, and contact leucoderma, mostly in young to middle-aged individuals. Contact anaphylaxis due to hair dye has also been reported.[37] The symptoms may begin within a few hours to 1–2 days after the application of the dye with itching, redness, papulation, and vesicles over the scalp, forehead, hairline margin, and around the eyelids. The severity may vary from mild itching to edema of the face and eyelids, blistering, and exudation. Lesions can also extend to the neck, upper chest, and upper arms and rarely, may become generalized. Men using hair dyes to color their beard and moustache may develop lesions over the face. Many patients complain of associated photosensitivity. Some patients may present with a predominant airborne contact dermatitis like picture with involvement of eyelids, retroauricular folds and flexures, especially cubital fossa. In severe cases, patients may present with prurigo-like lesions on the extensor aspect of extremities. Although less common, allergic reactions to hair dye have also been reported in children.[38] These are mostly adolescent children in the age group of 12-15 years who get sensitized after an exposure to temporary henna tattoos.

Rarely, adverse reactions to hair dye can present with a non-eczematous morphology. Hospital *et al,* reported a lymphomatoid contact dermatitis to PPD containing hair dye, which was proven on patch testing.[39] Matterne *et al,* diagnosed body dysmorphic syndrome in a hair dresser who despite having proven sensitivity to PPD continued to expose herself to the allergenic hair dyes as she was dissatisfied with the appearance of her hair.[40] Jain *et al,* found lenticular changes in 89% of the 200 hair dye users compared to 23% in the control group with an additional 7% developing early presbyopia and concluded that hair dye is potentially toxic to human lens, an observation, which was confirmed on animal experiments.[41] In addition, the prolonged effect of PPD exposure has been associated with renal impairment. Hamdouk studied the long term effects of PPD exposure in a group of 72 hairdressers and observed high prevalence of renal impairment (14%), proteinuria (26.4%), and hematuria (41.1%). Hypertension, skin changes, and bronchospasm were seen in 19.4%, 38.9%, and 22% of females, respectively.[42]

Depigmentation due to contact sensitivity to PPD occurs over the scalp, extending beyond the hairline onto the neck. Ghosh *et al,* studied 864 patients presenting with chemical leucoderma, and found hair dyes to be the putative agent in 27.4% of cases.[43] Hydrogen peroxide present in hair dyes may cause structural hair damage. Additives, such as pyrogallol and resorcinol, are other potential allergens. Penchalaiah *et al,* studied the sensitizers commonly causing contact dermatitis from cosmetics in India.[44] Of 436 patients, 31 (7.1%) were suspected of having cosmetic dermatitis due to hair dyes. Of 34 patients in whom patch test was done, 20 patients had clinical diagnosis of contact dermatitis to hair dye and 8 (23.5%) showed positivity to 1% PPD. However, this study had its limitations as only a small number of patients were patch-tested. Wachsmuth

et al, reported loss of eyelashes with the use of mascara containing PPD.[45]

Oxidation hair dyes have emerged as a major cause of suicidal poisoning in India in recent years.[46] Classically, hair dye poisoning presents with cervico-facial edema, severe rhabdomyolysis, and renal failure. Poor prognostic factors include late presentation to the hospital, patients in whom no gastric lavage was done at the primary-care center, those requiring tracheostomy/intubation at the primary center, presentation with a low Glasgow Coma Score or seizures, established renal failure, and those who subsequently required dialysis, mechanical ventilation or an intensive care. Another area of concern is the association of use of hair dyes and malignancies. Although there are some reports of positive associations, based on current data; overall evidence linking personal use of hair dyes to various leukemia and myelodysplastic syndromes (MDS) subgroups is weak, one cannot definitively rule out an association.[47] Harling *et al,* found a statistically significant increased risk (1.3 - 1.7 times) for bladder cancer among hairdressers, especially those in jobs for 10 years more although the results were confounded to an extent by large number of smokers in the population studied.[48]

DIAGNOSIS OF ALLERGIC CONTACT DERMATITIS TO HAIR DYES

Epicutaneous patch test remains the gold standard to confirm the contact allergy to hair dyes. The allergenicity of 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. Individuals allergic to PPD have a significant frequency of simultaneous sensitivity to chemically-related clothing dyes. Active sensitization from standard PPD patch testing although well-known, is not common.

PPD may show cross sensitization with other substances.[49] Azo dyes, used in semi-permanent and temporary hair dyes, ballpoint pen inks and as coloring agent in foods and medications, may cross-react with PPD, and it has been assessed that 20% – 28.5% of patients sensitized to textile dyes also have positive reactions to PPD. Exposure to azo dyes from shoes may cause foot dermatitis and cross-sensitization to PPD. 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. Drugs like benzocaine and procaine, sulfonamides, sulfones, sulfa drugs, para-amino benzoic acid and para-amino salicylic acid cross react with PPD. To avoid allergic reactions to hair dyes, an open test (or dab test) is recommended 48 hours before the hair coloring procedure. Krasteva *et al,*[50,51] studied the sensitivity and specificity of the consumer open skin allergy testing to predict the possibility of contact dermatitis to hair dyes.[50,51] Test products containing increasing concentrations of PPD (0.1, 0.5, 1.0, or 1.5%) were applied to 34 PPD-positive hair dye-allergic individuals and to 49 non-allergic control subjects. Allergic reactions were elicited in all PPD-positive subjects, whereas none occurred in control PPD-negative subjects. It can be concluded that the skin allergy test is a suitable tool for the secondary prevention of contact allergic reactions to hair coloring products.

Kneilling *et al,*[52] have established an *in vitro* assay to diagnose PPD allergy. Freshly-isolated peripheral blood mononuclear cells (PBMC) are cultured with titrated concentrations of PPD with or without IL-2 supplementation, and cell proliferation is determined by [3H]-thymidine incorporation.[52] Lymphocyte activation test (LAT) is used to detect PBMC cell proliferation specific to PPD, with at least 3.5-fold increase in [3H]-thymidine uptake required for a patient to be labeled as PPD allergic. PPD-LAT with IL-2 supplementation has demonstrated a sensitivity of 100%, remains unresponsive in controls not sensitized to PPD, and in those sensitive to other p-amino compounds.

TREATMENT AND PREVENTION OF ALLERGIC CONTACT DERMATITIS TO HAIR DYES

The causative hair dyes should be withdrawn. Regular use of sunscreens over sun-exposed areas with SPF 30 should be advised to those who manifest photosensitivity. Additional protection with use of appropriate clothing and wide brim hats is helpful. Symptomatic relief can be achieved with the use of topical steroids in lotion formulation, although care should to be taken to avoid super-potent steroids on face and their prolonged use to prevent the adverse effects. In severe cases, short course of systemic steroids may be required. Systemic anti-histamines to counter the itching may be needed. Pure henna can be substituted

for hair dyes. Hydroxyethyl-p-phenylenediamine sulfate (HPPS), itself a known sensitizer, has been investigated as a dyeing alternative for patients who are sensitive to PPD.[53] In a study, 40 of 216 (19.9%) patients reacted to 1% PPD, whereas only 2/216 (0.9%) showed a positive reaction to 1% HPPS and 2.3% to 2% HPPS.

Recommended strategies for the prevention of hand dermatitis in hairdressers include improved education, appropriate glove use, and the application of after-work moisturizing creams. Nixon *et al*,[54] conducted a population-based study involving 193 trainee hairdressers and 184 practicing hairdressers to assess their knowledge of skin hazards, the skills they practiced, and the frequency of glove use.[54] Knowledge of skin hazards was poor in both groups. The use of gloves was inadequate, particularly when performing work. Lee *et al*,[55] investigated the permeation behaviors of 2% p-aminophenol (PAP), 2% m-aminophenol (MAP), 2% o-aminophenol (OAP), and 4% PPD with disposable natural rubber latex (NRL) gloves, disposable polyvinylchloride (PVC) gloves, and neoprene (NP) gloves. Breakthrough times were 4 hours for NRL and PVC gloves and more than 8 hours for NP gloves, which was not hastened with the use of hydrogen peroxide.[55] Based on these observations, it can be concluded that disposable NRL gloves and disposable PVC gloves should not be used repeatedly for handling the hair dye products.

CONCLUSIONS

Although the data implicating hair dyes as a potent allergen and a potential mutagen is quite strong, the ultimate decision whether to dye one's hair or not lies with the individual. Going by the ever increasing sale of hair dyes in the market, it appears that the general public tends to ignore these serious adverse effects in favor of a better appearance. Hence, it becomes even more important to create awareness among the people regarding the appropriate use of these cosmetics as per manufacturer's guidelines and to report the adverse effects as early as possible. At the same time, an appropriate legislation is required so that the concentration of the allergens is kept at a minimal possible level before it reaches the consumer.

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