

EDUCATION AND DEBATE

Addressing the conundrums of *p*-phenylenediamine hair dye allergy by applying Friedmann's principles of contact sensitization

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In the first conundrum, permanent hair dyeing involves the use of aromatic amines such as *p*-phenylenediamine (PPD), whose oxidation is pivotal to the dyeing process, but also generates potent allergens. Despite prolonged efforts by industry to search for safer alternatives, hair dyeing is still reliant on this type of aromatic amine. In the second conundrum, patch testing with 1% PPD remains the most useful screen for hair dye contact allergy. However, there is a very small but real risk of actively sensitizing the patient. Lowering the PPD concentration below 1% significantly reduces test sensitivity and diagnostic utility. Here, we argue that by applying Friedmann's principles of contact sensitization each conundrum can be addressed from a new perspective. These principles indicate that, when the exposed area of skin is small ($<1 \text{ cm}^2$), induction of contact allergy is sharply reduced, whereas elicitation of allergy is unaffected. Careful reflection on this principle suggests that we can predict where hair dye sensitization is most likely to occur, indicates a strategy to reduce the chance of contact sensitization occurring in consumers as a result of hair dyeing, and how we might mitigate the risk of active sensitization resulting from diagnostic patch testing.

KEYWORDS

contact sensitization, hair dye, patch testing, *p*-phenylenediamine

1 | INTRODUCTION

Between 1981 and 2010, Professor Peter Friedmann was involved in a classic series of experiments involving contact sensitization and establishing several principles governing the circumstances whereby contact sensitization occurs.¹ Here, we look at one crucial principle, that above 0.8 cm^2 the induction of contact allergy is determined by "dose per unit area" of skin exposure to a contact allergen, whereas, below this area, the total dose is also crucial in determining whether active sensitization occurs.

2 | DOSE OF ALLERGEN PER UNIT AREA OF EXPOSED SKIN DETERMINES SENSITIZATION FROM $\geq 0.8 \text{ CM}^2$

In a series of human experiments in which 2,4-dinitrochlorobenzene (DNCB) was used to induce skin sensitization,^{2–5} Friedmann's group varied both the surface area and the concentration of allergen, so that,

in some instances, the dose per unit area was the same despite the use of different surface areas or different concentrations. The key results are summarized below.

Using a fixed application area of 7.1 cm^2 and varying the dose, they found a graded sensitization response related to dose per unit of surface area of DNCB exposure. A $71 \mu\text{g}/\text{cm}^2$ DNCB exposure (and above) led to 100% of individuals becoming sensitized, a $35.4 \mu\text{g}/\text{cm}^2$ exposure led to 83% of individuals becoming sensitized, a $17.7 \mu\text{g}/\text{cm}^2$ exposure led to 63% of individuals becoming sensitized, and a $8.8 \mu\text{g}/\text{cm}^2$ exposure led to 8% of individuals becoming sensitized.

In a related experiment, when a sensitizing dose of $250 \mu\text{g}$ of DNCB was applied to a surface area of 7.1 cm^2 to give a dose per unit area of $35.4 \mu\text{g}/\text{cm}^2$, 83% of individuals were sensitized. When a sensitizing dose of $62.5 \mu\text{g}$ of DNCB was applied to a surface area of 1.8 cm^2 , also giving a dose per unit area of $35.4 \mu\text{g}/\text{cm}^2$, a closely comparable proportion, 86%, were sensitized.

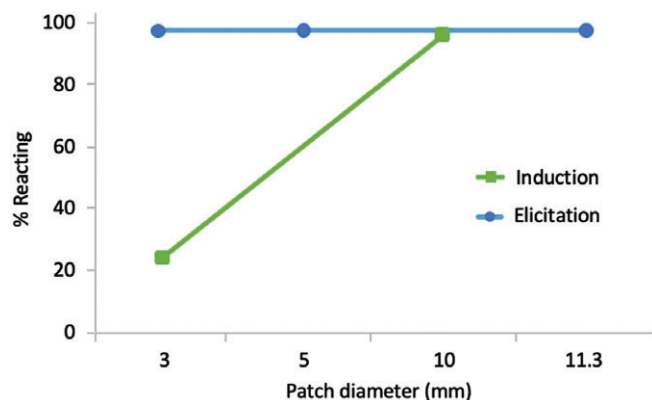


FIGURE 1 Literature data on the effect of patch diameter on induction and elicitation. With decreasing diameter of the patch test, elicitation remains unchanged while the risk of sensitization decreases

A series of experiments showed that the “dose per unit area” was robust and reproducible. As noted by Friedmann, “Over a wide range of areas—from a circle of 4.25 cm in diameter down to 1 cm—if the dose per unit area (of DNCB allergen) remained constant, there was no effect of area, even though the total doses varied by up to tenfold.”

An important exception to this rule occurs when the surface area of skin is reduced to below 0.8 cm² (a circle 1 cm in diameter). A dose of 30 µg of DNCB applied to a skin area of 0.8 cm², with a subsequent concentration of 38 µg/cm², resulted in 93% of individuals being sensitized. However, a dose of 3 µg applied to a skin area of 0.08 cm² with exactly the same dose per unit area value of 38 µg/cm² resulted in only 26% of individuals becoming sensitized ($P < 0.001$) (Figure 1).⁴ Friedmann¹ concluded that these results can be explained by absolute Langerhans cell (LC) numbers.¹ With a mean density of 59 000 LCs per cm² of skin, and with up to 20% of LCs migrating into the dermis (approximately 6000–12 000 LCs), this number is sufficient to fully sensitize a human.¹

3 | APPLICATION OF FRIEDMANN'S PRINCIPLE

3.1 | Reducing sensitization resulting from hair dye use

3.1.1 | Oxidation; a requirement for both the hair dyeing process and sensitization

It has long been recognized that oxidation is an important part of the hair dyeing process, converting colourless chemicals into agents reflecting colour and enabling binding to hair protein.⁶ A coupler allows polymerization within the hair shaft.⁷ Oxidation, however, is also involved in the allergic sensitization process. Aeby et al studied the sensitizing properties of *p*-phenylenediamine (PPD) and its oxidative products by measuring dendritic cell activation and responses in the local lymph node assay (LLNA).⁸ PPD was unable to activate dendritic cells in vitro. Although PPD gave a positive response in the LLNA, this was consistent with the use of an already oxidized sample (oxidation will begin within minutes); when the time of exposure was decreased so that autooxidation was unable to occur, the LLNA was

negative for sensitization. PPD was unable to activate dendritic cells in vitro, in an assay that did not allow for oxidation. In contrast, dendritic cell activation was observed after PPD was chemically pre-oxidized or air-oxidized. As a further control, acetylation of PPD resulted in no activation. The authors concluded that oxidation of aromatic amines such as PPD was a prerequisite for sensitization. Pot et al concluded that oxidation was required for the haptenization properties of hair dye molecules.⁹

3.1.2 | Clinical presentation of allergic contact dermatitis

The usual mode of presentation for allergic contact dermatitis caused by aromatic amines such as PPD is a dermatitis reaction to hair dye applied to the scalp. In a minority of cases, the presentation results from exposure to aromatic amine in a so-called temporary “black henna” tattoo or as hand dermatitis resulting from occupational exposure in hairdressers.¹⁰ Occasionally, presentation occurs as a non-dermatitic rash.¹⁰ Allergic contact dermatitis caused by PPD is usually located on the head and neck. However, the areas typically involved are, rather than the scalp, regions of non-hair-bearing/glabrous skin. Sites include the forehead, ears, neck, and periorbital areas.¹¹ This may not be surprising when one takes into account the surface area of hair, which greatly exceeds the area of the skin surface bearing that hair. Consequently, most of the hair dye applied to the scalp will be absorbed onto and into the hair.¹⁰ Therefore, in practice, the “dose per unit area” will be greatest along the scalp margins.

3.1.3 | Likely site of sensitization to hair dye

As there is no hair to absorb the bulk of the dose of oxidized hair dye chemical on non-hair-bearing/glabrous skin, the dose per unit area of hair dye chemical at this site would be expected to be much higher than that applied to the scalp skin. As expected, the allergic contact dermatitis reaction (ie, the elicitation reaction) on areas of the head and neck is off, but typically adjacent to, the hair-bearing scalp. One of Friedmann's principles is that, as long as the surface area exceeds 1 cm², sensitization is determined by dose per unit area. The sensitization phase would be most likely to also occur, therefore, on the areas of skin off the scalp (ie, the forehead, ears, and neck), as the area involved is likely to be >1 cm².

Such a consideration opens up an avenue for prevention, or at least diminution, of hair dye sensitization. Oxidation is required for effective hair dyeing. However, as hair dye sensitization is most likely to occur on areas of skin around the scalp, rather than on the scalp itself, prevention of oxidation, or at least reducing the level of oxidation of the hair dye on these skin sites, will reduce the likelihood of the induction of sensitization. Indeed, application of an antioxidant before cutaneous application of PPD does reduce the availability of the allergen,¹² and ascorbic acid/vitamin C has been shown to reduce the intensity of elicitation reactions in individuals with a proven history of PPD contact allergy.^{12,13} Therefore, a reasonable avenue to pursue, in order to reduce sensitization resulting from hair dye use, is the application of antioxidant on and around the scalp before and after hair dye application to the scalp.

3.2 | Reducing the risk of active sensitization resulting from patch testing with PPD

Screening for hair dye allergy is performed by patch testing with PPD 1% pet. in most baseline series of contact allergens. This represents the most effective simple screen for hair dye allergy. For the hair dye allergens, reactions in the absence of a concomitant positive reaction to PPD are very rare, except for toluene-2,5-diamine sulfate (PTD), for which cross-reactivity is $\approx 80\%$.^{14,15} Thyssen et al¹⁶ reviewed the median prevalence of PPD sensitization among dermatitis patients, which was 4.3% in Asia, 4.0% in Europe, and 6.2% in North America.¹⁶ According to the Information Network of Departments of Dermatology (IVDK) ($n = 3307$), if such results were extrapolated to the general population, the prevalence of positive reactions to PPD would be $\approx 1\%$.¹⁷ A study of >10 000 people from the normal adult population of five European countries found a prevalence of contact allergy to PPD of 0.8%.¹⁸ Patch test screening of 2545 normal adult volunteers in Bangkok showed a prevalence of PPD allergy of 2.7%, which, when extrapolated to the general population, suggested that more >1 million Thai adults may be sensitized to PPD.¹⁹ Therefore, hair dye allergy is common in both the patch test clinic and the normal population. Furthermore, patients with hair dye allergy do not necessarily present with a definitive history. In one study of patients presenting with dermatitis and who had positive patch test reactions to PPD, one in three did not report a history of reacting to hair dyes.²⁰ Allergy to PPD may present in a diverse manner, including exacerbation of pre-existing dermatitis, lichenoid dermatitis, mimicking angioedema, erythema multiforme-like reactions, and pseudolymphomatoid and pigmentary changes.¹⁰

Given the above considerations, the inclusion of PPD in a baseline screen for contact allergens remains justified, as it is a common cause of allergic contact dermatitis; use only in targeted testing would be difficult, in view of both the common lack of a positive history and the potentially diverse presentations. However, there is a controversy over whether PPD 1% pet. should be included in the baseline series, as there is a potential risk of active sensitization. Our data from repeat patch testing with 1% PPD of patients 6 months after the first patch testing with 1% PPD suggests that one in 600 patch tests may result in active sensitization.¹⁹ A further large retrospective study of 1035 patients who had been patch tested twice showed no significant difference in PPD allergy rates from those in patients patch tested for the first time ($n = 12\ 265$), implying no significant rate of active sensitization.²¹ In contrast, in a study of 63 patients, Devos found low relevance for late patch test reactions to PPD, estimating that as many as 7.9% of patients could have developed active sensitization.²² Although the consensus is that active sensitization does not occur frequently,²³ another group from Germany estimated that there were late reactions in 1.5% of the tested population ($n = 1428$), some of which could be attributed to active sensitization (though some of these reactions were recorded from self-reporting by telephone interviews). Consequently, PPD 1% pet. was withdrawn from the German baseline contact allergen screening series.²⁴ Furthermore, the self-testing by consumers for hair dye “as is,” which is the industry standard for pre-screening, could potentially lead to active sensitization solely by this process.²⁵ Although the use of PPD is limited in hair dye

products to a maximum concentration of 2% on the head, there is potential for a relatively high dose per unit area in self-testing (estimated to be well in excess of the diagnostic patch test for dark hair dye shades), combined with frequent exposure.^{25,26}

To combat the risk of active sensitization, some groups have tried reducing the PPD patch test concentration. However, reducing the concentration of PPD significantly reduces the test sensitivity. Geier et al²⁷ found that reducing the concentration of PPD in the patch test from 1% to 0.3% reduced the sensitivity of detecting contact allergy to PPD by 26%.²⁷ The alternative approach is to utilize Friedmann's “principles”. Below a diameter of 1 cm, the surface area becomes critical—induction is highly dependent on area at small diameters. Induction of sensitization is critically determined by dose per unit area, down to 0.8 cm, but, as shown by Fischer, elicitation is not affected by area (Figure 1).²⁸ Thus, in 15 individuals with known allergy to PPD, patch tests elicited comparable results when applied on patches 2, 3, 4 or 8 mm in diameter.²⁹ Reducing the surface area for patch testing may not only protect against active sensitization to PPD, but could also apply to testing with other potent allergens, for example, acrylates.

4 | LIMITATIONS OF THE PAPER

As in any theoretical paper, the selected circumstances used to illustrate key scientific principles may, in the real-life situation, be subject to other practical and unquantified factors. For example, although still governed by the dose per unit area considerations already mentioned, repeated low-dose exposure may act as a sensitizing stimulus.³⁰ Furthermore, in real life, the risk of sensitization from exposure to uncoupled agents remaining on the hair in the days or weeks after dye application has not, to our knowledge, been fully quantified and would not be fully protected against. Likewise, our suggested steps would not protect against occupational exposure, although it should be possible to apply the knowledge in this respect. Although patch testing with PPD is acknowledged as the main screening method to detect hair dye allergy, it is certainly not 100% sensitive; limiting the area of patch test exposure to other additional hair dye screening agents used would also be necessary to minimize the risk of active sensitization resulting from patch testing.

5 | CONCLUSION

Attempts to reduce or even eliminate contact sensitization from hair dyeing have so far proven to be unsuccessful. Reducing the risk of active sensitization from diagnostic patch testing without reducing the sensitivity of the test has also so far proven unsuccessful. Application of Friedmann's principles of contact sensitization allows novel perspectives to pursue means of reducing sensitization from hair dyeing and also reduce the risk of active sensitization from both patch testing and self-testing for hair dye allergy. We are persuaded that the evidence indicates that the application of antioxidants, such as vitamin C, to the skin adjacent to hair-bearing sites would mitigate the risk of sensitization from PPD. Reduction of the area of exposure in

diagnostic patch testing and consumer testing would help to minimize the risk of active sensitization while still alerting to PPD contact allergy.

CONFLICTS OF INTEREST

John P. McFadden, David A. Basketter and Ian R. White are directors of HDS Ltd, a non-trading company devising methods for reducing contact allergy.

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