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The 2-Methoxymethyl Modification of *p*-Phenylenediamine Reduces the Sensitization Risk for Hairdressers to Hair Dyes—An Occupational Hand Exposure–Based Risk Assessment

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Background: **Allergic contact dermatitis involving the hands is a common occupational skin disease for hairdressers and the potent sensitizers *p*-phenylenediamine (PPD) and toluene-2,5-diamine (PTD) are associated with the development of occupational allergic contact dermatitis.**

Objective: **The aim of the study was to analyze whether the use of the moderate sensitizer 2-methoxymethyl-PPD (ME-PPD) in professional hair dyes is a suitable tool to reduce the occupational contact allergy risk for hairdressers.**

Methods: **Hand exposure of hairdressers (N = 11) to ME-PPD was analyzed under routine hair coloring conditions in commercial salons. By accounting for wet work and uneven hand exposure, the daily hand exposure was derived and compared with the occupational acceptable exposure level (AEL), that is, the sensitization induction threshold of ME-PPD adjusted for interindividual variability among workers.**

Results: **The daily hand exposure to ME-PPD was 1.6 μg/cm^2, and the occupational AEL was 215 μg/cm^2. The ratio of hand exposure to AEL was calculated as the margin of safety (MOS) against occupational sensitization. For ME-PPD, the MOS of 134 indicates a low likelihood of sensitization versus PPD and PTD with MOS values of 2.7 and 5.9, respectively.**

Conclusions: **Our data predict that the use of ME-PPD in professional hair color products improves the protection of hairdressers against hair dye–related contact allergy versus the use of PPD and PTD.**

Allergic contact dermatitis (ACD) is one of the most common occupational skin diseases, and the hairdressing profession is at an elevated risk.[1–3] Allergic contact dermatitis often already develops during apprenticeship and is facilitated by the combination of the exposure to potent sensitizers, such as the oxidative hair dye precursors *p*-phenylenediamine (PPD) and toluene-2,5-diamine (PTD), and in the setting of wet work.[4,5] Once allergic hand dermatitis has developed, it more frequently results in change of profession or not remaining in the workforce conferring a high severity and worse prognosis of occupational hand dermatitis.[6–8] Consequently, the reduction of occupational exposure to potent sensitizers is considered particularly important in the development of prevention strategies for hairdressers.[4]

Regarding the role of hair dyes in occupational hand dermatitis, a recent sensitization risk assessment for hairdressers indicated that allergy induction cannot be prevented because the daily hand exposure to PPD or PTD is close to their sensitization thresholds.[9] Correspondingly, recent patient data confirm that PPD and PTD remain contact allergens of prime concern for allergic hand dermatitis among hairdressers.[4,10–13]

A significant reduction of the sensitization potency in the local lymph node assay (LLNA) from extreme to moderate was achieved by introducing a methoxymethyl side chain into PPD, resulting in 2-methoxymethyl-PPD (ME-PPD).[14] Hence, the replacement of PPD or PTD by ME-PPD enabled formulation of hair dyes with a low likelihood of consumer sensitization in line with the primary prevention principles.[14] A series of cross-elicitation studies with a total of 73 PPD-allergic patients showed a clearly limited reactivity to ME-PPD: While under simulated hair dye use conditions, more than 80% reacted to PPD, 62% did not react when PPD was replaced

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by ME-PPD, and another 18% showed a reduced reaction strength to ME-PPD.[15–18] The limited cross-reactivity in PPD-allergic patients and the moderate skin sensitization potency in the LLNA are both consistent with an impactful alteration of the PPD structure by the methoxymethyl side chain that likely causes a reduced rate of recognition by T cells from PPD-allergic patients and possibly also by naive T cells.[14,16,18]

We hypothesize that the use of the moderate sensitizer ME-PPD in professional hair dyes instead of the potent sensitizers PPD or PTD is a suitable tool to reduce the occupational contact allergy risk for hairdressers. For this purpose, we firstly analyzed the daily hand exposure to ME-PPD under typical working conditions in commercial salons mainly using ME-PPD–containing hair colorants. We then assessed whether the hairdressers' daily hand exposure is sufficiently below the sensitization threshold of ME-PPD to avoid sensitization particularly considering occupational risk factors, such as wet working conditions, in a quantitative risk assessment (QRA). Finally, we compared the QRA outcome for ME-PPD with published data for PPD, PTD, and resorcinol[9] to demonstrate how the use of ME-PPD in professional hair dyes contributes to reduce the risk of allergic hand dermatitis for hairdressers.

MATERIALS AND METHODS

Subjects and Hair Coloring Work Flow

Eleven hairdressers working at 3 different hairdressing salons (2 in the greater Frankfurt/main region and 1 in the greater Cologne region, Germany) participated in the study that was undertaken from September 2018 to August 2019. The salons participated on a voluntary basis, and individual hairdressers were recruited as volunteers during personal visits. Two hairdressers reported skin problems, that is, atopic dermatitis and histamine-mediated skin inflammation. None of the hairdressers reported contact allergy symptoms, and no diagnostic patch test data were available. The mean age was 40 years (range, 22–57 years); there were 10 female hairdressers and 1 male hairdresser. They had worked as hairdressers for 5 to 40 years (mean, 20 years). The salons varied in size and employed between 3 and 12 hairdressers.

Salons were visited during regular working hours. Hand rinse sampling was performed at least during 1 complete hair color service per hairdresser including documentation of the hair color product(s) applied. In some cases, sampling was possible during up to 3 complete services.

A complete hair color service consists of the following working steps: first, the hair color tint is mixed with the developer in a bowl using the application tool, that is, the brush. The mixture (the final hair color product) is brushed on the client's hair and remains on the client's hair for approximately 30 minutes. Next, the hairdresser rinses the hair with water and washes it with shampoo, may apply a conditioner, and dries it with a towel. Finally, the hairdresser cuts and/or styles and blow-dries the client's hair.

For differentiation of the individual hairdresser's hands, the hand holding the working tool (eg, brush, scissors, comb) is referred to as the dominant hand, and the other hand is referred to as the serving hand. The individual use of gloves was documented.

Hair Color Products

The hair color products used in the commercial hairdressing salons were from the professional hair color product line Koleston Perfect^{ME+} from Wella, the only commercially available professional product with ME-PPD. The applied ME-PPD concentration was dependent on the hair color shade (or mixture of shades) selected by the individual hairdresser for the client. The ME-PPD concentration range of the applied shades and the frequency of applications in that range are summarized in Table 1. All shades contain typical formulation ingredients, such as fatty alcohols, surfactants, and solvents, whereas the addition of further hair dye ingredients is specific for the individual color selected.

Setup for Exaggerated Hair Coloring Conditions

For this purpose, the concentration of ME-PPD was increased from the maximum 1.2% in commercial products to 1.8% for the experimental product (after mixing with the developer) representing the maximally allowed use concentration in the European Union (EU).

Three female hairdressers (mean age, 40 years [range, 35–45 years]; mean years of working in profession, 16 [range, 14–18 years]) from the Wella internal test facility (Darmstadt, Germany) participated in the study. None of the hairdressers reported contact allergy symptoms, and no diagnostic patch test data were available.

Each hairdresser performed 3 consecutive complete hair color services with the experimental product (following the same working steps as described for commercial salons) to 3 artificial training heads for hairdressers (L'Image, Neusäß, Germany) with implanted human hair of typical hair density. During each phase of the hair color service, training heads were placed at the typical position of a client head. Glove use was documented.

Reagents

The ME-PPD (CAS: 337906-36-2) standard was provided by the Wella Dye Capability (Hünfeld, Germany). Potassium dihydrogen phosphate, potassium hydroxide 2M, ethanol 96%, hydrochloric acid, sodium borate, sodium ascorbate, and ascorbic acid were purchased from Merck (Darmstadt, Germany). High performance liquid chromatography (HPLC) grade water was obtained from the Milli-Q A10 Water system (Merck, Darmstadt), and HPLC grade acetonitrile was obtained from J.T. Baker (ThermoFisher Scientific, Darmstadt, Germany). Syringe filters CHROMFIL GF/PET,

TABLE 1. ME-PPD Concentrations and Use Frequency of Applied Hair Color Products*

No. Shades	Average ME-PPD Concentration After Mixing With Developer	Tonal Shade Range
4	1.0% ± 0.2	Dark/medium dark
8	0.5% ± 0.1	Medium light
5	0.15% ± 0.1	Light

Based on selection by hairdressers (N = 11) for application of full color services to clients.

ME-PPD, 2-methoxymethyl-p-phenylenediamine.

25 mm, 1 μm/0.45 μm were obtained from MACHEREY-NAGEL (Düren, Germany).

Hand Rinse Sampling Procedure

Hand rinse sampling was performed similarly to the procedure described by Lind et al.[19,20] Briefly, hand rinse solution was prepared fresh the morning of the experiment by mixing 10% ethanol and 90% of a 0.05M borate buffer with adjusted pH 8.0, containing 0.2M ascorbic acid. Gloves were removed before the hand rinsing step, and samples of the dominant and serving hands were collected separately. During the hand rinsing step, each hand was rinsed vigorously for 2 minutes in a polythene bag containing 50 mL of rinsing solution. Aliquots (3–4 mL) of these solutions were transferred to amber glass vials and immediately stored in a portable refrigerator, before being transferred to the laboratory freezer (−72°C). Samples were filtered using a syringe filter, before analysis.

HPLC Analysis

The HPLC system was a 1290 Infinity II LC System (Agilent Technology, Waldbronn, Germany), consisting of a quaternary HPLC pump, a vacuum degasser, a temperature-controlled oven, an autosampler, and a diode array detector. Instrumental control, data acquisition, and data processing were provided by OpenLab ChemStation C01.07 SR3 (Agilent Technology). For chromatographic separation, a Purospher RP18e LiChroCart column (Merck, Darmstadt, Germany) was used.

Chromatographic separation was performed on an RP18 column as described before with 0.02M potassium dihydrogen phosphate buffer adjusted to pH 7.0 (A) and acetonitrile (B) as mobile phase and a column temperature of 40°C. The flow rate was set at 1.2 mL/min, and the injection volume was set at 10 μL. The HPLC was programmed to start with a gradient elution that went from 2% to 10% B in the first 15 minutes, followed by a second gradient from 10% to 70% B in the next 5 minutes. The 70% B concentration was kept for 5 minutes. Finally, the column was flushed with 98% B for 5 minutes and then reconditioned for additional 5 minutes (total run time of 35 minutes). 2-Methoxymethyl-*p*-phenylenediamine was detected on a diode array detector at a detection wavelength of 210 nm with a 4-nm band width and reference wavelength switched off. In addition, UV spectra from 200 to 640 nm were stored. 2-Methoxymethyl-PPD was quantified by external calibration with standard solutions in the concentration range from approximately 0.2 to 4 μg/mL in a 9:1 mixture of A and B. Unequivocal identification of ME-PPD in sample solutions was achieved by comparison of retention time and UV spectrum. The limit of detection and the limit of quantification resulted in 2 and 14 μg/hand, respectively.

RESULTS

Estimation of the Occupational Hand Exposure of Hairdressers to ME-PPD per Working Day

Typical occupational exposure of hairdressers to ME-PPD from professional hair color products was assessed based on hand rinses obtained from hairdressers (n = 11) from 3 different commercial salons using a hand rinse sampling and HPLC detection of ME-PPD.

Concentration ranges of ME-PPD in the hair color products applied by the participating hairdressers during the different hair color services are summarized in Table 1. The data show that products from all shade ranges were used including 4 products of the darkest shade range containing the highest ME-PPD concentrations commercially available, that is, up to 1.2% after mixing with the developer.

The use of gloves and their quality were captured during the work flow of each complete hair color service: For preparing the final hair color product by mixing the color cream with the developer in a bowl, none of the 11 hairdressers used gloves, and 9 of the 11 hairdressers were subsequently putting on polyethylene gloves for applying the final hair color to the client's hair using a brush as application tool. All hairdressers were using gloves for the rinsing/shampooing and conditioning step (8 used polyethylene, 3 used nitrile gloves) and subsequently performed cutting, styling, and/or blow-drying without gloves.

Correspondingly, individual separate hand rinse samples of the dominant and serving hands were taken (a) after applying the final hair color product and (a) after cutting, styling, and/or blow-drying of the client's hair. In addition, a sample of each hand was taken as a reference value before starting the hair color service. This way, a total number of 66 hand rinse samples of all relevant hand exposures before and during a hair color service were collected without substantially interfering with the routine work flow. All 22 samples taken before the hair color service were below the limit of detection of 2 μg/hand. For the dominant hand and the serving hand, 15 and 14 of the 22 samples, respectively, were above the detection limit. The use of gloves did not significantly impact hand exposure during the product application step likely because of the use of the application tool. The mean hand exposure to ME-PPD per working day is 62.6 μg based on the sum of steps (a) and (b) for both hands. The maximal value observed for both hands per working day is 160.6 μg (Table 2A).

Estimation of the Hairdresser Hand Exposure to ME-PPD Under Exaggerated Hair Coloring Conditions

Three hairdressers from the Wella test facility performed 3 consecutive complete hair color services (following the same working steps as described for commercial salons) to 3 artificial training heads using a hair color product containing 1.8% ME-PPD. This is an increase in the ME-PPD concentration by 33% compared with the highest concentration in marketed products of 1.2% (Table 1).

In line with the habits in commercial salons, no gloves were used for preparing the final hair color product by mixing the color cream with the developer, whereas all 3 were using vinyl gloves for applying the final hair color and for the rinsing/shampooing step. All hand rinse samples taken before the first hair color service were below the limit of detection. Exposure of both hands after applying the final hair color product was 105 ± 84 and 459 ± 161 μg/cm^2 after cutting/styling/blow-drying with bare hands. In summary, the mean

TABLE 2. Daily Occupational Hand Exposure of Hairdressers (N = 11) to ME-PPD

A. Residues in Hand Rinse Samples,* μg

	Dominant Hand		Serving Hand		Sum	Maximal Value
Panelist	Application	Cutting/Styling	Application	Cutting/styling	Application + Cutting/ Styling of Both Hands	
1	9.8	7.7	5.8	bd		
2	bd	bd	bd	bd		
3	bd	8.9	bd	14.8		
4	11.4	bd	16.8	bd		
5	46.8	18.6	29.2	13.8		
6	18.7	9.1	20.1	22.1		
7	8.9	9.7	10.8	26.1		
8	bd†	7.1	bd†	8.1		
9	6.9†	58.5	8.9†	8.9		
10	7.7	27.5	8.2	14.7		
11	bd	15.4	bd	7.7		
Mean (range)	15.7 (6.9–46.8)	18.1 (7.1–58.5)	14.3 (5.8–29.2)	14.5 (7.7–26.1)	62.6	160.6

B. Estimation of Daily Hand Exposure

	Exposure of Both Hands, μg				
	Working Day‡	Adjustment for Overestimation by Rinsing§	Adjustment for Wet Working Conditions‖	Exposed Surface Area of Both Hands,¶ cm^2	Daily Hand Exposure, $\mu g/cm^2$
	161	16.1	161	100	1.6

C. Distribution of ME-PPD Between Skin Rinses and Skin Exposure

Skin Source	Applied Dose,# $\mu g/cm^2$	Skin Rinse (Surface Excess Rinsed Off), %	Measured Exposure Level** (MEL; = Skin Exposure After Rinsing in SC+ Epidermis + Dermis + Receptor Fluid), %	Ratio of Skin Rinse to MEL	Reference
Human	378.6 ± 5.4 (equivalent to 1.8% in product)	98.4 ± 5.0††	2.7 ± 0.8	36	Goebel et al[14]
Pig	347.8 ± 31.4 (equivalent to 1.8% in product)	92.9 ± 1.6‡‡	2.5 ± 0.9	37	SCCS[21]

**Using hair dye products with ME-PPD concentration ranges provided in Table 1. Hand rinse samples of the dominant and serving hands were taken from each of the participating hairdresser after application of the final hair color product and after cutting, styling, and/or blow-drying of the client's hair.*

†No gloves used during application.

‡Taken from Table 2A (maximal value rounded up).

§Application of factor of 0.1 to account for relation between amount in skin rinse and amount relevant for skin sensitization (see Table 2C).

‖Based on the study by the World Health Organization.[22]

¶Adjusted for uneven hand exposure during hair dyeing procedure.[9]

#Applied dose of [^{14}C]-labeled ME-PPD (microgram equivalents per square centimeter in approximately 20 mg/cm^2 hair dye product considered as 100%) to human skin and pig skin samples (values were calculated form the experimentally applied dose of 100 mg/cm^2); percentage of applied radioactivity in skin rinses after 60 (††) or 30 (‡‡) minutes, (**) in SC and compartments representing systemic exposure at 24 hours after application.

*bd, below limit of detection of 2 μg/hand; ME-PPD, 2-methoxymethyl-p-*phenylenediamine; MEL, measured exposure level; SC, stratum corneum; SCCS, Scientific Committee on Consumer Safety.

highest hand exposure to ME-PPD theoretically possible was 564 μg for both hands.

This represents a 3.5-fold increase of the maximal hand exposure to ME-PPD found under realistic use conditions of commercial products, that is, from 160.6 to 564 μg, and although unlikely to occur in real workplace scenarios, it can serve as a theoretical estimate for extremely high ME-PPD hand exposures.

Estimation of Relevant Skin Exposure to ME-PPD From Hand Skin Rinse Samples

For estimating the relevant skin exposure to ME-PPD from hand rinse samples, the relation between the concentrations considered not to contribute to biological effects (surface excess) and the concentrations remaining on and in the skin after rinsing, that is, the measured exposure level (MEL), was compared (Table 2C). Data

from in vitro dermal absorption experiments with ME-PPD applied under realistic hair dye use conditions to human and pig skin were used.[14,21] The relation between applied dose, skin rinse fraction (surface excess), and MEL is compiled in Table 2C. The ratio of skin rinse to MEL is consistent among the 2 available experiments, that is, 36 and 37, respectively. This indicates that the skin exposure on hairdressers' hands is considerably lower than the ME-PPD concentration in the rinsing samples. Correspondingly, the concentration in the hand rinses needs to be adjusted for the relevant skin exposure. A conservative adjustment factor of 0.1 was used in line with our previous work considering the ratio of skin rinse to MEL for 3 other hair dyes with a range from 15 to 79.[9]

Estimation of the Exposed Hand Surface Area

Estimation of the hairdresser hand surface area exposed during the hair color service is critical for the occupational risk assessment and has been performed previously.[9] It was driven by conservatively accounting for ethnic and sex differences among hairdressers, such as a smaller size of female hands, and for uneven distribution during the working step of cutting, styling, and drying because it is generally performed without gloves. Because only a limited area of the palm surface including the fingers is in touch with the remaining hair color on the rinsed hair, an exposed area of 100 cm^2 for both hands was considered to provide a conservative adjustment accounting for the expected uneven distribution during that phase. Because the risk assessment for skin sensitization is based on dose per unit area of skin comparisons, the smaller the exposed hand area used, the higher the hair dye dose per unit area becomes. Consequently, using an area of 100 cm^2 for both hands is 8 times more conservative than the standard hand surface area of 860 cm^2 commonly used for dose per unit area calculations of hand exposure to cosmetic products.[23]

Application of the Skin Sensitization Potency Information for ME-PPD

The no expected sensitization induction level (NESIL) is defined as the quantitative threshold exposure level considered not to induce skin sensitization in humans.[24] It represents the toxicological threshold that is used as the point of departure for the QRA. The NESIL for ME-PPD of 1075 μg/cm^2 has been established based on data from an LLNA that has been evaluated by the EU Scientific Advisory Board, the Scientific Committee of Consumer Safety, and is compliant with highest regulatory standards.[21] Assessment factors accounting for uncertainties regarding matrix effects were not considered relevant because of the use of dimethylsulfoxide as vehicle with skin penetration enhancing and irritating properties compared with the hair dye product matrix as previously described.[14,25]

DISCUSSION

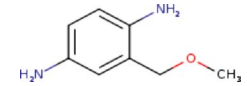
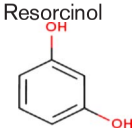
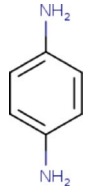
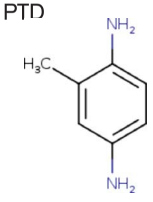
The daily hand exposure of hairdressers to ME-PPD has been assessed in line with the skin sensitization risk assessment principles[22,26] by considering the typical occupational habits and practices for hair color services. Correspondingly, hand exposure was analyzed from 11 hairdressers from 3 commercial salons in Germany mainly using Koleston Perfect^{ME+}, the ME-PPD–containing professional hair color product line from Wella. Hand rinse samples were taken (*a*) after applying the final hair dye product (gloves used by 9/11) and (*b*) after cutting, styling, and/or blow-drying of the client's hair (no glove use). These work steps have previously been shown to represent the relevant hand exposures during hair color services under realistic work conditions including typical professional glove-wearing practices.[9,20,27]

Our hand rinse data indicate that the average hand exposure to ME-PPD per working day is 62.6 μg and that the maximal value observed is 160.6 μg (Table 2A). Both values are considered as providing realistic estimates for the daily hand exposure to ME-PPD, because the hair dye products used are well distributed over the concentration ranges commercially available for ME-PPD (Table 1). In addition, the age and experience ranges of the participating hairdressers cover a wide range (age, 22–57 years; 5–40 years in profession). Furthermore, the average and maximal values for ME-PPD are well within the range of published values for occupational hand exposures to PPD, PTD, and resorcinol with an average from 31.8 to 95.2 μg and with maximal values from 136.8 to 192.2 μg.[9,20]

The individual steps to derive the daily hand exposure in dose per unit area from the hand rinse data are provided in Table 2B and are in line with the QRA approach previously described for occupational exposure to hair dyes.[9] First, a factor of 0.1 was used to correct for the overestimation of the ME-PPD concentration in hand rinses versus the amount that remains on and in the skin available for skin sensitization (referred to as the MEL; for details, see Table 2C). Application of the factor of 0.1 is also consistent with the previous risk assessment considering the ratio of skin rinse to MEL for 3 other hair dyes.[9] Second, a factor of 10 was used to account for the prolonged exposure to wet work[22] associated with an increased likelihood of impaired skin barrier integrity and of ACD due to concomitant exposure to irritants and allergens.[28–30] Third, the resulting values were divided by 100 cm^2 representing the surface area of the hairdressers' hands/fingers that is directly exposed to the freshly colored hair during cutting, styling, and/or blow-drying, as previously described.[9] Correspondingly, the daily hand exposure in dose per unit area under realistic working conditions is 1.6 μg/cm^2 (Table 2B).

The skin sensitization potency information for the occupational risk assessment for ME-PPD is summarized in Table 3 in comparison with the potency information for resorcinol, PPD, and PTD. Applying the human potency categorization principles outlined by Basketter and coworkers,[31] ME-PPD is considered to belong to the same category as resorcinol (category 4), that is, substances requiring considerable/prolonged exposure to higher dose levels to produce sensitization. Resorcinol is a benchmark for this category because of the low frequency of human sensitization, despite its widespread use at high levels in hair dyes. Like ME-PPD with a NESIL of 1075 μg/cm^2,[14] also resorcinol is considered a moderate skin

TABLE 3. Skin Sensitization Potency and Hairdresser Hand Exposure Data of ME-PPD for Margin of Safety Calculation Compared With Resorcinol, PPD, and PTD

INCI Name (Abbreviation), Structure	Skin Sensitization Potency Category		NESIL, μg/cm^2	Occupational AEL, * μg/cm^2	Hairdresser Daily Hand Exposure, μg/cm^2	Margin of Safety (AEL/ Daily Hand Exposure)
	Based on Human Data[31]	Based on SCCS Assessments				
ME-PPD 	nd	**Moderate**[21]	1075 (see Goebel et al[14])	215	1.6†	134
Resorcinol 	**Infrequent cause of contact allergy** in relation to level of exposure; benchmark substance for category 4	**Moderate** – Clinical studies show that the frequency of contact sensitization in humans is low.[32]	917.5 (see SCCS[32])	183.5	1.4 (see Goebel et al [9])	131
PPD 	**Extensive evidence of contact allergy** in relation to degree of exposure and size of exposed population; benchmark substance for category 1	**Extreme** – Extremely potent contact allergen in animals – Important and frequent allergen in consumers – Allergic reactions to it may be severe. – Continued use in hair dyes remains a considerable concern for consumer safety.[33]	27.5 (see Goebel et al[25])	5.5	2 (see Goebel et al[9])	2.7
PTD 	**Frequent cause of contact allergy**, but of less significance compared with category 1; assigned to category 2	**Extreme** – Frequency of allergic reactions in hairdressers and consumers remains a considerable concern for consumer safety.[34]	41.3 (see Goebel et al[14])	8.3	1.4 (see Goebel et al [9])	5.9

**Occupational AEL = NESIL divided by 5 to adjust for interindividual variability among workers as recommended by the European Chemical Agency.*[35]

†Taken from Table 2B.

*AEL, acceptable exposure level; INCI, International Nomenclature of Cosmetic Ingredients for free base; ME-PPD, 2-methoxymethyl-p-*phenylenediamine; NESIL, no expected sensitization induction level; nd, not done; PPD, *p*-phenylenediamine; PTD, toluene-2,5-diamine; SCCS, Scientific Committee on Consumer Safety (Scientific Advisory Board of the European Union).

sensitizer based on its NESIL of 975 μg/cm^2.[32,36] In contrast, the human potency category for PPD is category 1, that is, substances with the highest intrinsic potency, and category 2 for PTD, that is, substances with a strong intrinsic potency.[31] This is reflected by their comparatively low NESILs between 17.5 and 27.5 μg/cm^2 for PPD and of 41.3 μg/cm^2 for PTD,[14,25,37] indicating that regular contact with low to moderate concentrations is likely to sensitize perhaps 1% to 10% of those exposed.[31] Correspondingly, safety concerns for hair dye consumers and hairdressers regarding the frequency and severity of allergic reactions to them are emphasized by the Scientific Committee of Consumer Safety, the EU Scientific Advisory Board[33,34] (Table 3).

The next step in the occupational risk assessment is to adjust the NESIL of ME-PPD for interindividual variability for professionals to obtain an occupational acceptable exposure level (AEL). In line with the European Chemical Agency recommendation, we applied the default factor of 5 (Table 3, column 4). Whereas the default factor of 10 was found adequate to adjust skin sensitization induction thresholds for interindividual variability among the general population[38] with more susceptible subpopulations, the factor of 5 is considered to adequately address the risk for workers compared with elderly or diseased individuals.[35,39] Because the risk of wet work conditions has been accounted for in the exposure assessment by a factor of 10 (Table 2B), no further assessment factors were applied in line with the previous risk assessment for hairdressers.[9,40]

The final step of the risk assessment is the comparison of the occupational AEL with the estimated daily hairdresser hand exposure (Fig. 1). The ratio of occupational AEL to daily hand exposure was calculated as an equivalent to the margin of safety (MOS), that is, the ratio between a point of departure (usually the no observed adverse effect level) and an estimate of the exposure.[23] The MOS values for ME-PPD of 134 and for resorcinol of 131 are very comparable (Table 3, column 5). This indicates that the likelihood of induction of occupational sensitization through ME-PPD is low, because resorcinol is not considered a relevant occupational allergen for hairdressers.[4,9,10,12] Furthermore, the use of ME-PPD in professional hair colors increases the MOS by 50 fold and 23 fold versus the use of PPD and PTD with MOS values of 2.7 and 5.9, respectively. Even under simulated exaggerated exposure conditions to ME-PPD leading to a 3.5-fold increased hand exposure, the MOS for ME-PPD of 38 clearly remained above the MOS values for PPD and PTD.

On the basis of the similarity of the MOS values between ME-PPD and resorcinol, we conclude that the use of ME-PPD in professional hair color products improves the protection of hairdressers against hair dye–related contact allergy versus the use of PPD and PTD under typical hair-coloring conditions, including the adequate use of protective gloves.

Correspondingly, recent patch test data for resorcinol confirm our prediction that high MOS values are in line with low sensitization frequencies considering the widespread use of resorcinol in professional hair dye products (see Table 4 and the study by Uter et al[41]). In contrast, recent patch test data for PPD and PTD confirm that occupational exposure of hairdressers to them can lead to sensitization and corresponding allergic hand dermatitis (Table 4) as expected from their comparatively low MOS values.

For the future, market surveillance data and prospective studies in hairdresser apprentices are suitable tools to evaluate to what

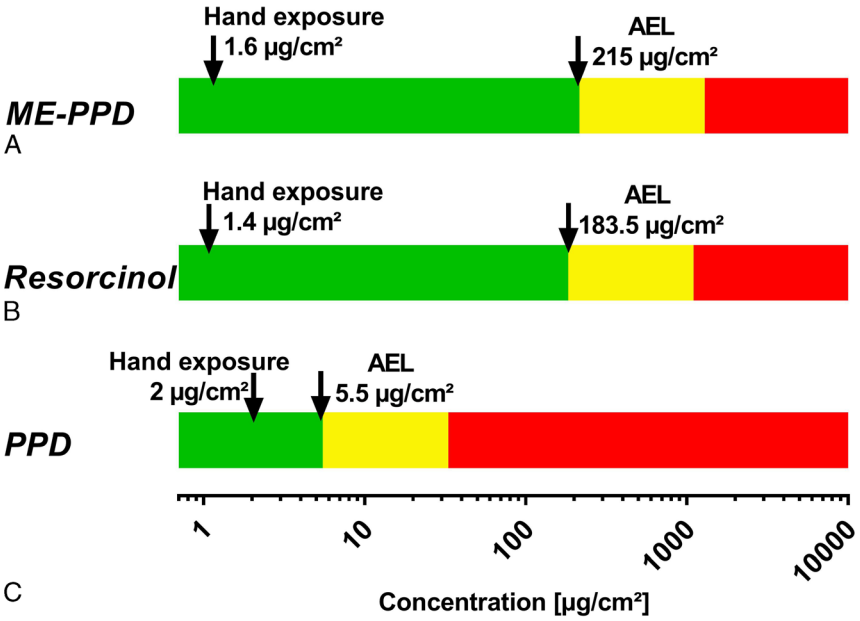


Figure 1. Logarithmic comparison of the occupational AEL for skin sensitization induction and the daily hairdresser hand exposure under typical working conditions considering adjustment for wet work (black arrows). Red bar: exposure considered to be associated with induction of skin sensitization; green bar: exposure not considered to be associated with the induction of skin sensitization; yellow bar: occupational AEL considers adjustment for interindividual variability among workers.

TABLE 4. Prevalence of Positive Patch Test Reactions to Selected Hair Dyes (Standard and Hairdressers Series) in Hairdressers

Number Tested	Hair Dye Precursor	Patch Test Positive	Hands as Site of Symptoms	Country	Study Period	Source
136	PPD	63 (46%)	123 (90%) ACD	Greece	2010–2019	Gregoriou et al[10]
	PTD	48 (35%)				
	Resorcinol	0				
264	PPD	62 (23.5%)	255 hand dermatitis/120 ACD	Germany, Austria, Switzerland	2007–2016	Brans et al[4]
	PTD	67 (25.2%)				
263 (post-NACDG reactions as 366 × 71. 9% hairdressers)	PPD	146 (39.9% of all occupational related dermatitis)	183 (78.9% of occupational dermatitis in hairdressers was located on the hands)	United States, Canada	2001–2016	Warshaw et al[12]
218	PPD	53 (24.3%)	Occupational dermatitis	Italy	1996–2016	Mauro et al[13]

ACD, allergic contact dermatitis; NACDG, North American Contact Dermatitis Group; PPD, p-phenylenediamine; PTD, toluene-2,5-diamine.

extent the use of ME-PPD supports the primary prevention of occupational hair dye–related contact allergy to PPD and/or PTD.

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