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Contact allergy to hair-colouring products: a cosmetovigilance follow-up study by four companies in Europe from 2014 to 2017

Background: A previous analysis of undesirable events (UEVs), reported to four major companies following the use of hair-colouring products in Europe, showed that the reporting rates were stable for both oxidative and direct hair-colouring products over the period 2003-2006. **Objectives:** In order to verify the impact of risk management measures implemented since 2006, as well as the impact of a new Commission Regulation (No 1223/2009), the same four companies analysed cosmetovigilance data collected over an additional four-year period (2014-2017). The objective was to determine whether there was any time effect, country effect, or product type effect, as well as identify risk factors. **Materials and Methods:** Each company collected reports of alleged UEVs, undesirable effects (UEFs) and serious undesirable effects (SUEs) for their products in their key European markets, and calculated the respective reporting rates (number of events/million units sold). A detailed analysis was performed on allergic contact dermatitis-type events. **Results:** The reporting rates for alleged UEVs and allergic-type UEFs associated with hair-colouring products remained stable over the four-year period, although a statistically significant decrease was observed for some companies. No time effect on SUEs was observed for three companies but a statistically significant decrease in SUEs was observed for one company. Black henna tattoos remained a major risk factor regarding SUEs due to hair dyes. **Conclusion:** The reporting rates of undesirable events, including contact allergy-type events, were stable over time. This was true for oxidative and direct hair dyes, for both home use and professional exposure scenarios.

Key words: Cosmetovigilance, hair-colouring products, allergic contact dermatitis, undesirable events, black henna tattoos

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Contact allergy to hair-colouring products remains a concern and surveillance data are regularly published in the dermatological literature. Most of the studies are carried out on consecutively tested eczema patients [1-4] and less frequently on the general population [5]. An analysis of undesirable events (UEVs) reported to manufacturers following the use of hair-colouring products in Europe over the period 2003-2006 was published by four major companies [6]. This showed that the reporting rates (number of events/million units sold) for UEVs, including contact allergy-type events, remained constant over the four-year period, both for oxidative and direct hair-colouring products.

In recognizing some of the safety concerns, the industry has limited the maximum on-head concentrations of extreme sensitizers, such as p-phenylenediamine (PPD) and p-toluenediamine (PTD), and gradually increased the safety labelling of hair-colouring products. In Europe, the Commission Regulation No 344/2013 [7] stipulates a decrease in on-head concentration of PPD from 3% to 2% and

introduced new safety warnings, some of which had been self-imposed previously by the industry. Product labels now include, besides the ingredient listing, warning statements that hair dyes may cause severe allergic reactions, products are not intended for children under the age of 16, and henna tattoos may increase the risk of allergy (Commission Regulation [EU] No 344/2013) [7]. The on-head concentration of PTD was decreased from 5% to 2% in two steps, starting from 2013. In addition to all these measures, the hair dye industry committed to only introducing new hair dyes with a sensitizing potential lower than that of some already marketed ingredients, such as PPD and PTD. An educational programme was developed, directed to users and hairdressers (*Colour well, colour wise, Cosmetics Europe* and *The facts about, the Cosmetic, Toiletry & Perfumery Association*) [8, 9]. The industry was also committed to harmonising the allergy alert test (AAT), an important precautionary measure recommended to be carried out by each consumer 48 hours before a hair-colouring procedure. A multicentre study was performed using the

harmonised AAT protocol, demonstrating its suitability to adequately alert consumers [10].

Independent of all the measures intended to enhance the safety of hair-colouring products listed above, a new cosmetic regulation came into force in 2013, making the reporting of serious undesirable effects (SUEs) to authorities by the Responsible Person (the cosmetic industry) and/or distributor (Regulation [EC] No 1223/2009) mandatory [11].

To verify the impact of all risk management measures put in place, cosmetovigilance data for hair-colouring products (over the period 2014-2017) was further evaluated by the same cosmetic companies involved in the study of Krasteva *et al.* (2010). As in the previous paper, these companies are referred to as Company 1, 2, 3 and 4 (corresponding to the same companies as those in the previous report). However, the hair-colour manufacturing activities of P&G have since been taken over by Coty.

The objective of the analysis was to determine whether there was any effect of time within the four-year period (a trend in increase or decrease of notified UEvS and effects), effect of country (significant difference between the countries included in the analysis) and effect of product type (direct vs oxidative hair dyes, professional vs home). Allergy-type events were also compared with the period 2003-2006.

Materials and methods

Spontaneous reporting and post-marketing surveillance procedures [12]

Cosmetovigilance is a post-marketing surveillance system based on the analysis of spontaneous reports. It is conducted via an integrated stepwise process requiring collection, monitoring and evaluation of UEvS.

A UEv is a human adverse health event that is voluntarily reported by a consumer, a healthcare professional, a regulatory authority or any other individual, which occurred during or after normal or reasonably foreseeable use of a cosmetic product, but is not necessarily attributable to the use of the product.

An UEf refers to an adverse reaction on human health, attributable to the normal or reasonably foreseeable use of a cosmetic product.

A reported UEv is considered an UEf if a causality assessment is performed that demonstrates a causal link between product use and the adverse reaction.

SUEs are those that result in temporary or permanent functional incapacity, disability, hospitalization, or congenital anomalies or present an immediate vital risk or death. Due to the potential medical seriousness, all SUEs, except those classified as “excluded”, are reported to the National Competent Authorities where the SUE occurred. The processes in place for collecting reports of UEvS are similar between the cosmetic companies concerned.

Complaints related to alleged intolerance are reported to dedicated services locally within companies in the respective countries. All available medical information concerning an initial complaint is collected, including the results of complementary investigations, if performed (such as patch tests in cases of suspected allergic reactions). It is important to underline that cosmetovigilance is mainly

based on consumer self-reporting and as such, not all the medical information required for reliable assessment is available in all cases. The reporting rate is based on the number of spontaneously reported UEvS (numerator) and the population exposure (denominator).

Causality assessment

Causality assessment is the analysis of the probability that a well identified product used by a consumer is responsible for a genuine UEv, *i.e.* whether the event is attributable to the use of a cosmetic product and should therefore be considered as a UEf. A standardized methodology should be employed. The cosmetic industry developed such a methodology in 2005 [13, 14]. The current algorithm used is that developed within the frame of the European Commission SUE Reporting Guidelines (SUE reporting guidelines) [15]. Causality is classified using a five-point scale for both methods.

All cases of alleged UEvS are entered into a centralized database. Thereafter, causality assessment is performed on a case-by-case basis, when feasible. The causal relationship between the use of a cosmetic product and the event can be qualified as: very likely, likely, not clearly attributable, unlikely or excluded, according to a decision table based on the following criteria: (1) the type of clinical reaction which may be more or less evocative of a skin disorder related to the use of the suspected cosmetic product; (2) the chronological sequence of events which may be compatible with the appearance of clinical manifestations characteristic of a particular skin disorder elicited by the product; and (3) the results, or absence, of specific medical investigations, or the result of re-exposure to the suspected product.

UEvS with a causality assessment of “likely” or “very likely” are classified as UEfS, and are considered to be reasonably attributable to product use.

Products

Included in the analysis were the following types of hair-colouring products:

- Oxidative (permanent, demi-permanent/tone-on-tone) hair dyes (approximately 80 to 90% of market share);
- Direct (semi-permanent and temporary) hair dyes (approximately 10% to 20% of market share).

Different brands of both types are marketed for home use and professional use. Company 4 markets only professional-use products; the remaining companies present data on both professional and home-use products.

Data collection and reporting rates

Each company collected alleged reports of UEvS, reported for their hair-colouring products in their key European markets during a four-year period, from 2014 to 2017. The rates were reported by each respective company. The reporting rates for products for a particular country were calculated as the number of UEvS and UEfS collected per million units sold over the period considered (a one-year or four-year period). The reporting rate for products for a particular year was calculated as the sum of all the countries’ UEvS and

UEfs collected during that year per million units of product sold for the same year. For a four-year rate (2014 to 2017), this was based on the total number of UEvs or total number of UEfs reported with hair-colouring products sold during the four years per million units sold. From these data, three main series of reporting rates were provided:

- (1) Reporting rates for all types of events with different levels of causality assessment of alleged UEvs. For the calculation of these rates, data were collected from 10 countries for Company 1, seven countries for Company 2, 23 countries for Company 3, and five countries for Company 4. These countries were selected by each company as key European markets.
- (2) Yearly rates of UEvs according to country were calculated for all hair-colouring products and, separately, for oxidative and direct hair-colouring products.
- (3) Reporting rates for UEfs (causality assessment “likely” and “very likely”) with manifestations compatible with allergic contact dermatitis. The method of calculation was the same as that mentioned above and the data were issued from the same number of countries for each company, as listed in (1). These rates were provided by each company for the four-year period and refer to oxidative hair-colouring products and direct-colouring products separately.
- (4) Specific analysis of UEvs and UEfs (causality assessment “likely” and “very likely”) related to the use of oxidative hair-colouring products in selected countries.

A detailed analysis was performed in order to investigate an increase in the rate of allergy to permanent (oxidative) hair-colouring products across the EU member states. The countries selected by each company fulfil the following criteria:

- each company has a large and/or stable sales market;
- the cosmetovigilance processes have been effective for a significant period.

For this specific analysis, data were issued from:

- three countries for Company 1 (UK, France, Germany);
- three countries for Company 2 (UK, France, Germany);
- four countries for Company 3 (UK, France, Germany, Sweden);
- five countries for Company 4 (UK, France, Germany, Netherlands, Austria).

The following (I to IV) reporting rates were calculated for each year from 2014 to 2017, for each selected country and, when feasible, for each product distribution network (home use or professional use):

- I) All types of UEfs to oxidative hair-colouring products.
- II) A breakdown of UEfs into allergic contact dermatitis and scalp and skin irritation.
- III) Serious cases of allergic contact dermatitis.
- IV) Allergic contact dermatitis following the application of black henna tattoos. The reporting rates concerning black henna tattoos were provided separately for serious and non-serious cases of allergic contact dermatitis.

All data were normalized against the units of product sold (number of UEv/million units sold).

Statistical methods

A statistical analysis was carried out for each company by an external organization (Soladis, Lyon, France). The time variable was introduced as a two-level class variable (2014-2015 and 2016-2017) in all models. The effect of time was analysed based on logistic regression for binominal data with time as a fixed factor. The comparison between 2016-2017 and 2014-2015 was performed for each country separately and for all countries overall for each company. Each type of event was analysed for oxidative and direct hair-colouring products.

The effect of country on oxidative hair-colouring products was analysed based on logistic regression with time and country as fixed factors. The comparisons between countries were performed for each type of event.

Reporting rates for different types of hair-colouring products (oxidative or direct) and distribution networks (professional vs home use for oxidative hair dyes) were analysed based on logistic regression with time and type of hair colouring as fixed factors.

The influence of having a black henna tattoo on the seriousness of allergic contact dermatitis to oxidative hair dyes was analysed by comparing prevalence rates of serious reactions between a population who has declared a black henna tattoo and a population who has not declared having black henna tattoo. The effect of black henna tattoos was analysed based on logistic regression with previous black henna tattoo (yes/no) as a fixed factor. The degree of freedom in this analysis does not allow overdispersion measurements, therefore significance should be considered with caution. Odds ratios and relative risk estimations were not affected. The comparison between the responses, “Yes” and “No”, was performed for serious allergic contact dermatitis events. The same analysis was also performed on pooled data from all companies (which did not pose a problem regarding overdispersion). In case of overdispersion, a William scale parameter was used. In case of quasi-complete separation of data (at least one of the comparison modalities had no event), Firth bias correction was used. For all the analyses, the threshold for statistical significance was 5%. Analyses were performed using SAS 9.4 software.

A descriptive analysis was performed to estimate the overall period effect (2014-2017 vs 2003-2006) for allergic contact dermatitis: all UEfs and serious UEfs.

Results

Reporting rates of all types of alleged UEvs (all types of events, all levels of causality assessment)

These results concern health-related complaints notified to the companies before any causality assessment was performed to determine which were reasonably attributable to product use. Following causality assessment, these rates correspond to all five levels of causality assessment.

Table 1. Reporting rates for UEVs (all levels of causality assessment) for all hair-colouring products and oxidative and direct hair-colouring products separately. Rates were calculated as the number of UEVs per million units sold.

		Year				4-year rate (2014 to 2017)
		2014	2015	2016	2017	
Company 1 (10 countries)	All products	3.8	3.1	3.7	2.9	3.4
	Oxidative	3.7	3.1	3.9	3.1	3.4
	Direct	6.8	2.5	2.0	1.5	2.5
Company 2 (7 countries)	All products	8.8	7.7	6.2	4.1	6.7*
	Oxidative	9.1	7.8	6.6	4.1	6.9*
	Direct	5.0	5.9	1.7	3.0	3.9*
Company 3 (23 countries)	All products	2.1	1.7	1.8	2.0	1.9
	Oxidative	2.1	1.7	1.8	2.0	1.9
	Direct	2.4	0.8	2.9	1.5	1.9
Company 4 (5 countries)	All products	2.0	1.5	1.0	0.8	1.3*
	Oxidative	2.4	1.7	1.0	0.9	1.5*
	Direct	0.2	0.2	0.5	0	0.2

UEv: undesirable event. *statistically significant decrease ($p < 0.05$) (effect of time).

Country yearly rates were calculated for all kinds of hair-colouring products together, and then for oxidative and direct hair-colour separately. The yearly rates for the four companies are shown in *table 1*. There was no time effect on the European area as a whole for Companies 1 and 3, for all hair-colouring products or for the two product types analysed separately. For Company 2, there was a statistically significant decrease for all hair-colouring products and for the two product types analysed separately. For Company 4, there was a statistically significant decrease for all hair-colouring products and for oxidative hair dyes, but there was no time effect on direct hair dyes. There was no statistically significant increase for any country when considered separately, for any of the four companies.

The UEv rates for direct hair-colouring products were significantly lower than those for oxidative hair-colouring products for two of the four companies; there was no statistically significant difference between product types for Company 1 and 3.

Reporting rates of UEVs with manifestations compatible with allergic contact dermatitis (causality assessment: “likely” and “very likely”)

These results concern notifications that, after causality assessment, were considered reasonably attributable to product use (UEfs) and which, furthermore, were associated with medical manifestations, chronological characteristics and ultimately medical investigations which were compatible with allergic contact dermatitis resulting from hair-colouring products. Reporting rates (per million units sold) are shown in *table 2*.

The analysis of these rates according to time showed that there was a statistically significant decrease in reporting

UEfs related to oxidative hair dyes for Company 2 and for direct hair dyes for Company 1. There was no effect of time on reporting allergic contact dermatitis related to oxidative hair-colouring products or allergic contact dermatitis related to direct hair-colouring products in three out of four companies. There was no statistically significant increase in reports for any country when considered separately, for any of the four companies.

Reporting rates for UEVs compatible with allergic contact dermatitis associated with direct hair-colouring products were significantly lower than those for oxidative hair-colouring products for Company 2 and 4; there was no effect of product type for the remaining two companies.

Specific analysis of oxidative hair-colouring products in selected countries

Time and country effect on UEVs and UEfs reported with oxidative hair-colouring products

The yearly reporting rates (per million units sold) for alleged UEVs (all levels of causality assessment) and UEfs (causality assessment: “likely” and “very likely”) reported with oxidative hair-colouring products for each company in selected countries are shown in *table 3*.

Time effect

Analysis of rates over time showed that there was a statistically significant decrease for Company 2 and Company 4 for both all alleged UEVs and UEfs. For Company 1, there was a statistically significant decrease in UEfs in the UK and France, with no effect of time when all countries were considered. There was no effect of time for Company 3. Countries with a statistically significant decrease are shown in *table 3*. There was no statistically significant increase in either all alleged UEVs or UEfs in any single country for

Table 2. Reporting rates for UEs with manifestations compatible with allergic contact dermatitis (causality assessment: “likely” and “very likely”) for oxidative and direct hair-colouring products. Rates were calculated as the number of UEs per million units sold.

		Year				4-year rate (2014 to 2017)
		2014	2015	2016	2017	
Company 1 (10 countries)	Oxidative	0.5	0.3	0.3	0.2	0.3
	Direct	0.9	0.3	0.1	0.1	0.2*
Company 2 (7 countries)	Oxidative	3.7	2.9	2.3	1.8	2.7*
	Direct	1.1	2.5	0.0	1.3	1.2
Company 3 (23 countries)	Oxidative	0.9	0.7	0.7	0.8	0.8
	Direct	2.2	0.6	1.8	0.9	1.3
Company 4 (5 country)	Oxidative	1.6	1.0	0.8	0.9	1
	Direct	0	0.2	0.5	0	0.2

UEf: undesirable effect. *statistically significant decrease ($p < 0.05$) (effect of time)

any of the companies. There was no statistically significant increase overall or for any of the countries for each company with regards to the reporting of UEs compatible with allergic contact dermatitis or serious UEs (*data not shown*).

Country effect

For Company 1, the reporting rates for allergic contact dermatitis (all UEs) were higher in France than in Germany ($p < 0.05$), while the reporting rates for serious UEs (“likely” and “very likely”) were higher in France and Germany than in the UK.

For Company 2, the reporting rates for all alleged UEs, all UEs and UEs compatible with allergic contact dermatitis were higher in Germany and the UK than in France ($p < 0.05$); the rates for all alleged UEs, all UEs and allergic contact dermatitis (all UEs and serious UEs: “likely” and “very likely”) were higher in the UK than in Germany ($p < 0.05$).

For Company 3, the rates of all alleged UEs, all UEs and UEs compatible with allergic contact dermatitis were higher in the UK than in France ($p < 0.05$). The rates of all alleged UEs and of allergic contact dermatitis (all UEs and serious UEs: “likely” and “very likely”) were higher in the UK than in Germany ($p < 0.05$). The rates of all alleged UEs, all UEs and UEs compatible with allergic contact dermatitis were higher in Germany and the UK than in Sweden ($p < 0.05$). The rates of all alleged UEs and UEs compatible with allergic contact dermatitis were higher in Germany than in France ($p < 0.05$).

For Company 4, the rates of UEs compatible with allergic contact dermatitis were higher in The Netherlands than in the UK, Austria, France and Germany.

Effect of the distribution network on reporting rates for alleged UEs and UEs due to oxidative hair-colouring products

This analysis was provided for Companies 1, 2 and 3. The breakdown of UEs and UEs with manifestations compatible with allergic contact dermatitis according to the distribution network (home use or professional) for each

country is shown in *table 4*, for each year from 2014 to 2017 and for the whole four-year period.

There was no effect of product type for Company 1. For Company 2, all alleged UEs and UEs compatible with allergic contact dermatitis were more frequent with home-use products ($p < 0.05$). For Company 3, all alleged UEs for UK, Germany and all countries together were more frequently associated with professional products; allergic contact dermatitis was more frequent with professional products in the UK ($p < 0.05$).

There was no effect of time for professional-use products except for Company 1, for which there was a statistically significant increase in the UK only for all alleged UEs. There was no effect of time on the reporting of alleged UEs for home-use products. A statistically significant decrease was found for reporting of UEs compatible with allergic contact dermatitis for Company 2 and 3 ($p < 0.05$).

Type of manifestations and effect of black henna tattoo on the severity of the reaction

UEs (causality assessment: “likely” and “very likely”) were analysed further according to the type of manifestation (chiefly scalp and skin irritation or allergic contact dermatitis) and severity of allergic contact dermatitis reactions. This breakdown is shown in *table 5*.

Serious UEs accounted for between 1.3% and 5.9% of all UEs notified to companies, in line with the previous period (notification rates of all UEs and serious UEs are shown in *table 3 and 5*, respectively). There was no effect of time on reporting of serious UEs compatible with allergic contact dermatitis, except for Company 2 (a statistically significant decrease was reported in the UK and all countries taken together; $p < 0.05$).

Overall, 132 serious UEs (SUEs) resulting from oxidative hair dyes, with manifestations compatible with allergic contact dermatitis (causality assessment: “likely” and “very likely”), were notified to the four companies over the four-year period in the three most populated European countries with the best performing cosmetovigilance systems (France, UK and Germany). In 43.1% of these cases, the seriousness criterion was “hospitalization”; the remain-

Table 3. Time and country effects on the reporting rates of alleged UEVs and UEfs for oxidative hair-colouring products. Rates were calculated as the number of events per million units sold.

		Alleged UEVs/million units sold					“Likely” and “very likely” UEfs/million units sold				
		2014	2015	2016	2017	4-year rate 2014 to 2017	2014	2015	2016	2017	4-year rate (2014 to 2017)
Company 1	UK	6.7	3.9	6.6	4.9	5.5	2.1	1.1	0.8	0.4	1.1*
	France	6.3	4.0	5.1	3.9	4.8	1.6	1.4	1.2	0.9	1.3*
	Germany	4.1	6.5	6.3	5.0	5.5	0.3	0.8	2.4	0.8	1.1
	The 3 countries overall	5.7	4.8	6.0	4.6	5.3	1.3	1.1	1.5	0.7	1.1
Company 2	UK	21.1	15.3	13.4	8.0	14.5	13.9	9.9	7.5	5.0	9.1*
	France	1.5	1.7	0.4	0.4	1.0*	0.7	0.9	0.0	0.4	0.5
	Germany	4.1	5.9	4.2	3.8	4.5	1.9	2.3	1.3	1.7	1.8
	The 3 countries overall	11.5	9.7	8.1	5.2	8.7*	7.2	5.6	4.1	3.0	5.0*
Company 3	UK	5.6	4.2	5.2	5.2	5.0	4.2	3.0	3.9	2.8	3.5
	France	2.8	2.0	2.9	3.3	2.7	1.4	1.3	1.8	1.6	1.5
	Germany	4.5	3.4	2.9	2.6	3.4*	3.7	2.8	2.6	2.2	2.8
	Sweden	1.7	1.2	2.6	1.7	1.8	1.4	0.9	1.3	1.2	1.2
	The 4 countries overall	4.2	3.1	3.2	3.1	3.4	3.3	2.4	2.5	2.1	2.6
Company 4	UK	0.2	0.6	0.4	0.4	0.4	0.2	0.2	0.4	0.4	0.3
	Netherlands	6.6	4.7	4.0	5.6	5.2	6.6	3.5	3.5	5.6	4.8
	France	1.8	0	1.8	0	0.9	0	0	1.8	0	0.9
	Germany	2.6	1.8	0.7	0.1	1.4*	2.1	1.2	0.6	0.1	1.1*
	Austria	0	0.7	0	0	0.2	0	0.7	0	0	0.2
	The 5 countries overall	2.4	1.7	1.0	0.9	1.5*	2.1	1.2	0.9	0.9	1.3*

UEf: undesirable effect; UEv: undesirable event; SUE: serious undesirable effect. *statistically significant decrease ($p < 0.05$) (effect of time)

ing cases were classified as SUEs on the basis of severe manifestations, self-declared or medically confirmed (with functional incapacity as a seriousness criterion).

In up to 33% of the serious UEfs, there was a known history of black henna tattoo application. However, in a significant number of cases, exposure to black henna tattoos could not be established as it was difficult to obtain an answer from consumers due to different reasons inherent to spontaneous reporting methods. In many cases, people were contacted directly by the company for a more detailed questionnaire. To better characterise the importance of black henna tattoos regarding serious UEfs resulting from hair-colouring products, the incidence of SUEs was compared between consumers with black henna tattoos and those without/did not reply, for each company and for all companies. The incidence of SUEs was calculated as follows:

– for consumers with known black henna tattoo applications, the percentage of people who had a serious reaction among all the people who had a reaction (serious or not serious) and who declared that they had a black henna tattoo application;

– for consumers with unknown or absent black henna tattoo applications, the percentage of people who had a serious reaction among all the people who had a reaction (serious or not serious) and who did not declare a black henna tattoo application.

Comparison between the incidence of serious UEfs in consumers with black henna tattoos and those without/did not reply (table 6) demonstrated a statistically significant difference for Company 1 and for the four companies together ($p < 0.05$). A history of black henna tattoo increased the risk of reporting a serious UEf associated with hair-colouring products (OR: 3.9; 95% CI: 1.0-14.6).

Comparison of allergic contact dermatitis-type response (“likely” and “very likely”) to oxidative hair-colouring products between 2014-2017 and 2003-2006

The two causality assessment algorithms used for the two periods share the same criteria for classifying UEVs as “likely” and “very likely” [6, 12, 14]. Therefore, the aller-

Table 4. UEs and UEs (allergic contact dermatitis) associated with oxidative hair-colouring products according to distribution network (professional use vs home use).

Alleged undesirable events/million units sold										Undesirable effects (ACD likely and very likely) / million units sold											
2014		2015		2016		2017		2014 - 2017		2014		2015		2016		2017		2014 - 2017			
Profess- ional use	Home use	Profess- ional use	Home use	Profess- ional use	Home use	Profess- ional use	Home use	Profess- ional use	Home use	Profess- ional use	Home use	Profess- ional use	Home use	Profess- ional use	Home use	Profess- ional use	Home use	Profess- ional use	Home use		
Company 1	UK	3.2	8.3	0.6	5.4	6.0	6.9	5.5	4.6	3.9	6.3	0.3	1.3	0.1	0.6	0.1	0.3	0	0.4	0.1	0.7
	France	7.6	5.2	4.1	3.9	4.6	5.4	3.1	4.8	3.9	4.8	1.0	0.7	0.7	0.7	0.9	1.0	0.5	0.5	0.8	0.7
	Germany	4.8	3.9	12.3	4.9	7.2	6.1	6.0	4.7	7.6	4.9	0.1	0.2	0.2	0.3	0.2	0.3	0.4	0	0.2	0.2
	3 countries	5.6	5.7	4.9	4.8	5.7	6.2	4.5	4.7	5.2	5.4	0.6	0.7	0.4	0.5	0.5	0.5	0.3	0.3	0.4	0.5
Company 2	UK	5.1	23.9	4.7	17.2	4.4	14.8	2.3	9.1	4.1	16.4	1.6	10.3	1.6	6.9	0.8	5.8	0.8	4.1	1.2	6.8
	UK	9.7	4.2	5.7	3.6	9.5	3.8	11.2	3.4	8.9	3.8	4.1	1.9	1.1	1.7	2.8	1.8	6.3	1.8	3.5	1.8
Company 3	France	3.6	2.5	1.4	2.2	2.8	2.9	6.4	1.9	3.5	2.4	1.0	0.6	0.7	0.7	0.5	1.3	2.1	1.1	1.1	0.9
	Germany	7.3	4.4	5.3	3.3	4.2	2.8	7.4	2.3	6.0	3.2	1.8	2.1	1.7	1.8	1.0	1.4	0.4	1.1	1.2	1.6
	Sweden	0	1.9	0	1.3	18.7	1.7	1.7	1.6	4.3	1.6	0	1.2	0	0.5	0	0.9	0	0.5	0	0.8
	4 countries	2.3	2.3	1.3	2.3	5.6	2.8	7.7	2.4	3.1	2.4	0.8	1.1	0.4	1.2	1.3	1.4	2.7	1.1	0.9	1.2

UEfs: undesirable effect; UEv: undesirable event.

Table 5. Type of manifestation associated with oxidative hair-colouring products and effect of black henna tattoos on the seriousness of the reaction. Rates were calculated as the number of UEs per million units sold.

		All UEs (likely and very likely)	Scalp and skin irritation	Allergic contact dermatitis	Serious UEs (ACD, likely and very likely)	Serious UEs with past history of black henna tattoos
Company 1	UK	1.1	0.5	0.5	0.03	0
	France	1.3	0.4	0.7	0.1	0.03
	Germany	1.1	0.7	0.2	0.08	0.01
	Total	1.1	0.6	0.5	0.07	0.02
Company 2	UK	9.1	2.8	6.0	0.4	0.0
	France	0.5	0.0	0.4	0.1	0.1
	Germany	1.8	0.4	1.4	0.1	0.0
	Total	5.0	1.5	3.3	0.2	0.01
Company 3	UK	3.5	0.8	2.2	0.4	0
	France	1.5	0.2	1.0	0.2	0.04
	Germany	2.8	1.1	1.6	0.2	0.02
	Sweden	1.2	0.3	0.7	0.1	0
	Total	2.6	0.8	1.5	0.2	0.02
Company 4	UK	0.3	0	0.3	0	0
	The Netherlands	4.8	0.2	4.6	0.2	0.1
	France	0.9	0.5	0.5	0	0
	Germany	1.1	0.4	0.7	0	0
	Austria	0.2	0	0.2	0	0
	Total	1.3	0.2	1.1	0.03	0.01

UEs: undesirable effect; ACD: allergic contact dermatitis.

gic contact dermatitis-type events reported during these two periods could be compared.

The reporting rates for UEs compatible with allergic contact dermatitis (all UEs and serious UEs) are shown in *figure 1* for each company separately and for each four-year period. Since not all raw data on UEs and sale numbers from the first period were retained by all of the companies, it was impossible to carry out a more detailed statistical analysis. However, an overall decrease in allergic reactions and serious allergic reactions related to oxidative hair dyes for three of the companies was observed, and this was reported in the same countries for two of these three companies (Company 1 and 3) during the two periods. An increase in all UEs compatible with allergic contact dermatitis was observed for Company 4, however, it is impossible to say whether the observed changes were significant. There was no increase in the reporting rates for serious UEs for any of the companies.

Discussion

This review of post-marketing UEv data for hair-colouring products, reported to the four major companies across

Europe over the period 2014-2017, contributes to the evaluation of occurrence of allergy in hair-dye users and identification of possible risk factors. UEs due to cosmetics are generally mild and transient and successfully managed by the consumer without medical intervention, thus not all UEs are seen as a ‘problem’ by the consumer, and therefore not reported to the company. More severe effects and especially SUEs are more likely to be reported by consumers and health professionals. As in all post-marketing surveillance systems, the extent of under-reporting in cosmetovigilance is unknown, however, under-reporting of SUEs is likely to be less significant than that of non-serious UEvs. Since 2013, cosmetic companies are obliged to notify all reported SUEs, except those with causality assessment “excluded” to the competent Authorities. The first statistical analysis of SUEs reported in the European Union (2014-2015) showed that hair-colouring and skin-care products stand out regarding the number of cases and the seriousness criterion leading to hospitalization [16].

Reporting rates are not incidence rates; they are, however, a useful indicator to identify and describe a signal. Caution should be taken in evaluating spontaneous reporting, especially when comparison is made between different countries

Table 6. SUEs in oxidative hair-dye consumers according to previous use of black henna tattoos.

	Company 1			Company 2			Company 3			Company 4			4 companies		
	Incidence (%)	Relative risk	OR (95%CI)	Incidence (%)	Relative risk	OR (95%CI)	Incidence (%)	Relative risk	OR (95%CI)	Incidence (%)	Relative risk	OR (95%CI)	Incidence (%)	Relative risk	OR (95%CI)
Serious UEfs in consumers with known black henna tattoo application	63.6			20.0			23.1			12.5			30		
SUEs in consumers with no black henna tattoos and in consumers who have not answered the question	12.2	5.2	12.6 (3.4 - 46.1)	6.9	2.9	3.3 (0.4 - 30.6)	18.8	1.2	1.3 (0.5-3.3)	1.9	6.6	7.4 (0.4-132.6)	11.8	2.5	3.9 (1.0-14.6)

SUE: serious undesirable effect; UEf: undesirable effect.

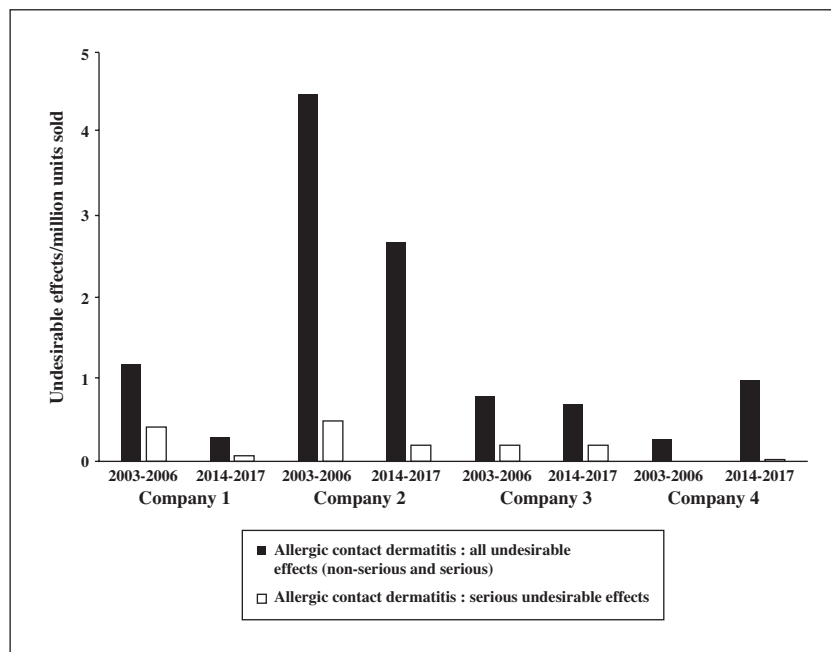


Figure 1. Allergic contact dermatitis-type effects (“likely” and “very likely”) due to oxidative hair-colouring products: 2014-2017 vs 2003-2006.

or between companies where cosmetovigilance systems are implemented differently. Differences in reporting rates do not necessarily reflect differences in product safety or in the efficiency of the underlying cosmetovigilance system. The rate at which cases are reported is dependent on many factors, including the time since the product was launched, cultural consumer habits regarding the reporting of UEs, media attention or environmental/public health concern and current national regulatory requirements for cosmetovigilance.

Analysis of the main parameters examined across companies

Review of several possible contributing factors on reporting rates such as time, country and type of products led to the following conclusions.

Time effect. There was an overall statistically significant decrease in events based on the first part of the analysis (all hair-colouring products in all studied countries) and on the second part (specific analysis on oxidative hair dyes in selected countries) for Companies 2 and 4 but no effect of time for Companies 1 and 3. The maintenance of the same trend in the first and second part of the analysis in the different companies can be explained by the inclusion by all companies of the most populated European countries, France, UK and Germany (218 million inhabitants), in both parts of the analysis.

The reporting rates for alleged UEs for all hair-colouring products (unselected consumer reports, all levels of causality assessment) were stable over the four-year period (2014-2017), except for a statistically significant decrease observed for Company 2 (all hair-colouring products) and Company 4 (oxidative hair dyes). In the same way, the

reporting rates for UEs, with manifestations compatible with allergic contact dermatitis (causality assessment “likely” and “very likely”), for all oxidative and direct hair-colouring products, also remained constant over the same period, except for a statistically significant decrease observed for Company 1 (direct hair-colouring products) and Company 2 (oxidative hair-colouring products). No effect of time was observed for serious UEs, compatible with allergic contact dermatitis, resulting from oxidative hair dyes, except for Company 2 (which demonstrated a statistically significant decrease). Comparison between the two four-year periods (2003-2006 and 2014-2017) revealed a similar trend in the rates for allergic reactions to oxidative hair dyes between the four companies, with a decrease in reporting in three of the four companies over time. The increased reporting rates for all UEs, compatible with allergic contact dermatitis for Company 4 may be due to the increased number of countries included in the second period and the inclusion of a country with comparatively high reporting rates (The Netherlands).

The overall decrease in allergic-type effects in the second period may be due to efficiency of the safety measures put in place between the two periods (decreased concentration of PPD and PTD, increased labelling, public campaigns about awareness of adverse effects of black henna tattoos and industry-led educational programs resulting in increased public awareness). However, this may also be due to the nature of spontaneous reporting. The first period (2003-2006) coincided with an accumulation of serious allergic contact dermatitis reactions to hair-colouring products in young individuals sensitized to black henna tattoos [17, 18]. These reactions were often misdiagnosed as life-threatening Quincke’s oedema and necessitated hospitalization and systemic treatment. This generated media

activity directed against hair-colouring products, thus creating conditions that favour the reporting of all kinds of effects following hair dye use. An increase in reporting rates was expected after the cosmetic regulations came into full force in 2013. We did not observe such an increase for any of the analysed UEs in the following years.

The observed trends require confirmation by dermatological networks. Based on the most recent multicentre study in Europe, the rate of contact allergy to PPD was shown to remain constant over the period 2002-2012 [3], and there is no published information thereafter.

Country effect. Yearly reported rates according to country (all alleged UEs and UEs compatible with allergic contact dermatitis due to oxidative and direct hair-colouring products) were largely unchanged, although a significant decrease was observed in some countries for individual companies.

Four-year reporting rates for oxidative hair-colouring products were similar for each company with some exceptions. Some reporting rates were statistically higher in the UK for two of the companies and higher in the Netherlands for one of the companies. For Company 1, reporting rates for allergic-type reactions were higher in France than in the UK, in contrast to the first four-year period. Historically, consumers in the UK have always had a higher rate of reporting of UEs for all types of cosmetic products. Despite standardization of the reporting of UEs, reporting rates are dependent upon the underlying cosmetovigilance systems which may be implemented differently in different countries within the same company.

Product type effect and effect of distribution network. In the first period (2003-2006), the reporting rates (UEs and allergic contact dermatitis-type UEs) for direct hair-colouring products was significantly lower than that for oxidative hair-colouring products. Based on the present analysis, the reporting rates of UEs for direct hair-colouring products were significantly lower for two of the four companies, and the reporting rates for allergic contact dermatitis-type UEs was significantly lower for only one company. No effect of product type was identified for the remaining companies. However, the fact that oxidative hair dyes are usually sold for a single application, while a “unit sold” of direct hair dyes can be used for one or multiple applications should be taken into consideration. If the number of applications of oxidative and direct hair dyes are considered, the rates for direct hair dyes would be much lower.

The comparison of reporting rates for oxidative hair dyes for home use versus professional products yielded inconsistent results. For one of the companies, allergic-type UEs were more frequent for home-use products, for one company they were more frequent for professional products, and for one company there was no effect of product type. The reporting rates are largely dependent on the processes in place for collecting UEs and they are different between home-use and professional products.

Black henna tattoos as a risk factor. The effect of black henna tattoos in the first period (2003-2006) was studied only based on 2006 data. The analysis of serious reactions reported in the second period (2014-2017) for

oxidative hair-colouring products confirms our finding of a statistically significant association with previous exposure to black henna tattoos for one of the companies and for the four companies together (OR: 3.9; 95% CI: 1.0-14.6).

The reason for this is widely recognized, as black henna tattoos contain various, sometimes extensive, amounts of PPD (up to 64%), or chemically related hair dye chemicals [19, 20]. A consumer, pre-sensitized by a black henna tattoo, will be at higher risk of eliciting a serious reaction when using a hair-colouring product containing PPD [21-24] and potentially cross-reacting colourants. There are more than 100 reports in the literature on sensitization to PPD associated with black henna tattoos [25].

The role of black henna tattoos in PPD sensitization has been confirmed in population-based studies [5] as well as consecutive eczema patients [26].

In recent years, the impact of black henna tattoos has been acknowledged by health authorities. From 2006, the last year of the first period of analysis, the French health authority conducted, over several years, a consumer awareness campaign on the risks associated with this practice [27]. In 2008, the European Commission launched a campaign in all member states to provide information to the public that black henna tattoos can cause serious health injuries [28]. Our data show that black henna tattoos remain a significant risk factor for SUEs and therefore efforts to inform the public should not be discontinued.

Conclusion

An analysis of UEs, reported following the use of hair-colouring products in Europe, was performed by four major companies over the period 2014-2017, after the European Cosmetic Regulation (EC) 1223/2009 came into full force in 2013. Although an increase in UEs may have been expected due to the obligation of reporting of SUEs to authorities, this was not the case based on the analyses of cases over the period 2014-2017. The reporting rates for UEs, including contact allergy-type events, remained constant. This was true for oxidative and direct hair-colouring products, for both home and professional-use products. For some companies, there was even a statistically significant decrease in specific types of UEs and effects in certain countries or all countries taken together within the four-year period (2014-2017). Based on comparison with the previous four-year period (2003-2006), all allergic-type UEs, including serious UEs, were shown to decrease. However, the conditions for data collection may have slightly changed in the meantime, which should be taken into account when comparing absolute figures between the two periods.

Some serious allergic contact dermatitis cases resulting from oxidative hair-colouring products have been documented. Analysis of these cases confirms our previous finding that a key contributory risk factor is previous black henna tattoo [6]. Further educational efforts are needed to guide hair-dye users on how to safely use hair-colouring products [8, 9]. ■

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