National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Hair dye allergy in consumers

Evaluation of the allergy alert test

Report 340300006/2011

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This investigation has been performed by order and for the account of Ministry of Health, Welfare and Sports and the Food and Consumer Product Safety Authority, within the framework of kennisvraag 5.1.5. Kennisbasis en advisering sensibilisatie”

Abstract

Hair dye allergy in consumers
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The allergy alert test advised by manufacturers of hair dyes in their instruction leaflets as a means of testing for hair dye allergy is inadequate in its present form. Standardization of the test protocols is required as these vary significantly between manufacturers. This is the conclusion drawn from the risk/benefit evaluation of the allergy alert test performed by RIVM. This evaluation was based on the current opinion of the SCCS (Scientific Committee on Consumer Safety), publicly available literature and interviews with experts in the field of skin allergy.

The induction of contact allergy and allergic contact dermatitis by oxidative hair dyes represents a significant health problem among consumers and hairdressers. In this context, the RIVM considers the allergy alert test in principle to be a valuable tool for assessing whether a specific hair dye product can elicit an allergic skin reaction in individual consumers. The instruction leaflets of hair dye products currently recommend that consumers always perform an allergy alert test 48 hours prior to each application of a hair dye product. In case of a positive test result, indicating a possible sensitivity to the hair dye product, consumers are advised not to apply the hair dye product and to seek medical advice to determine the cause of the reaction.

Whether consumers are able to adequately perform and evaluate an allergy alert test is unknown at the present time. It is therefore recommended that the industry further investigates this. It is also recommended that a campaign be launched with the aim of creating more awareness among consumers and hairdressers of the potential risks associated with the use of hair dyes.

Keywords:
hair dye allergy, evaluation, allergy alert test

Rapport in het kort

Allergie voor haarkleurstoffen bij consumenten
Evaluatie van de allergietest

De huidige allergietesten voor haarverf die consumenten via de productinstructie aangeboden krijgen, voldoen niet. In deze testen blijkt namelijk veel variatie voor te komen. De test moet dan ook worden gestandaardiseerd. Dit blijkt uit onderzoek van het RIVM, waarin de voor- en nadelen van de allergietest voor consumenten zijn geëvalueerd. Dit is gedaan op basis van de bestaande opinie van de SCCS (de Europese wetenschappelijke commissie voor consumentenveiligheid), openbare literatuur en interviews met deskundigen.

Het RIVM vindt het in principe waardevol dat consumenten van haarverf via de productinstructie wordt geadviseerd eerst een test te doen om vast te stellen of zij voor dit product allergisch zijn. Huidallergie veroorzaakt door haarverf is immers een groot probleem, zowel voor consumenten als kappers. Producenten van haarverf geven in de productinstructie het advies om 48 uur vóór het gebruik van de haarverf te testen of er sprake is van een overgevoeligheid. Deze allergietest is slechts een alarmsignaal waarmee consumenten worden gewaarschuwd om hun haren niet te verven. Ook wordt hen geadviseerd om een dermatoloog te bezoeken voor verder medisch onderzoek.

Tevens blijkt dat niet bekend is of consumenten de test zelf goed kunnen uitvoeren en interpreteren. Aanbevolen wordt dit nader te onderzoeken. Daarnaast wordt aanbevolen om onder consumenten en kappers meer bewustwording te creëren over de risico's van haarverf, bijvoorbeeld door middel van informatiecampagnes.

Trefwoorden:
haarverfallergie, evaluatie, allergie alert test

Contents

Summary

The use of hair dyes has become more and more popular during the last decades. An important health problem related to the use of oxidative hair dyes is the induction of contact allergy and allergic contact dermatitis. The majority of substances in oxidative hair dyes are potent skin sensitizers and the allergic reactions that are evoked can be very severe. To protect consumers against these allergic reactions, hair dye products contain safety instructions that include a warning that hair colourants can cause allergies. Furthermore, consumers are advised to always perform an allergy alert test (also referred to as skin alert test or self test) 48 hours before application of the hair dye product.

The Scientific Committee for Consumer Safety (SCCS) has evaluated this allergy alert test and concluded that although the test might offer protection to some individuals, the use of the test as it is currently proposed by industry would lead to misleading and possibly false-negative results.

The Ministry of Health, Welfare and Sport (VWS) and the Food and Consumer Product Safety Authority (nVWA) required a further evaluation of the benefits and risks of the allergy alert test. In this evaluation the SCCS opinion was used together with data from publicly available literature. In addition, the opinions of experts in the field, including dermatologists and the Dutch Cosmetics Association (NCV), have been taken into account. The aim of this report is to provide an overview of the risks and benefits of the allergy alert test and to make recommendations for further development of this test in the context of protecting consumers from the development of hair dye allergy.

The most well-known skin sensitizer in hair dyes is p-phenylene diamine (PPD), which is a very potent skin sensitizer that is present in different standard patch test series. It has been estimated that the prevalence of PPD allergy in the general European population ranges from 0.3-1%. In patients with allergic contact dermatitis the prevalence is 4-7%. The severity of allergic reactions differs greatly between subjects with a hair dye allergy. Severe cases can suffer from facial oedema and might require hospitalization, whereas others only experience mild rashes and can continue hair dyeing.

Currently, the safety instructions of hair dye products inform consumers about the potential risks of dyeing their hair and about factors that may increase the risk of developing an allergic reaction. The manufacturer also advises consumers to always perform an allergy alert test 48 hours before using the hair dye product. In case of an abnormal skin reaction, such as itching, redness or swelling, the product should not be used and consumers should seek medical advice.

The advice to perform an allergy alert test was initiated by COLIPA, the European Cosmetics Association. No specific guidance was proposed on how this test should be performed and, as a consequence, the instructions vary significantly between manufacturers. The most important differences are: the duration of exposure, which ranges from 45 minutes to 48 hours; the application site, which is either the skin behind the ears or the crook of the elbow, and the test material, which is either the hair dye alone or the mixture with hydrogen peroxide. The impact of the lack of standardization on the accuracy of the allergy alert test is unclear. Moreover, it is unknown whether consumers would

adequately perform an allergy alert test. Because of these issues, the SCCS concluded in their opinion that the test in its current form cannot be supported. Furthermore, the SCCS is of the opinion that diagnosing allergic contact dermatitis should be performed by a dermatologist. Finally, the SCCS is concerned about the induction of sensitization and believes that the test could result in false-negative outcomes, thereby misleading consumers.

The procedure of the allergy alert test and the possible risks and benefits for consumers were discussed with a two dermatologists and with the Dutch Cosmetics Association. There was no consensus on the benefits of the allergy alert test among the consulted dermatologists. It was acknowledged that the test can be helpful, but only if the test is simple to use and if the test procedure is standardized. Furthermore, the test procedure should reflect the actual use situation, meaning that the exposure duration should be in line with the application time of hair dyes. The test should also be performed with the mixture of the hair dye and hydrogen peroxide. Dermatologists questioned whether consumers are able to adequately perform an allergy alert test. Moreover, concerns were raised because the allergy alert test may lead to induction of sensitization and would lead to additional exposure to allergens.
The Dutch Cosmetics Association stated the opinion that consumers should always perform an allergy alert test before each product use. They supported the idea that that the test should be further developed and standardized by COLIPA.

In conclusion, based on the literature, the SCCS's opinion and interviews with field experts the allergy alert test is appreciated as a potentially valuable tool to assess if hair dye could elicit an allergic reaction. It is important to note that this test should be regarded an alert and not a diagnostic tool. However, in its current form the allergy alert test cannot be recommended, since the test needs to be further developed and standardized. Besides this, it should be further investigated whether consumers are able to perform and evaluate an allergy alert test. In addition, it is recommended to launch a public campaign to create more awareness under consumers and hairdressers on the potential risks of hair dyeing.

1 Introduction

In our modern society, the use of hair dyes has increased considerably. Many of the currently allowed hair dye ingredients are skin sensitizers, which are able to induce allergic contact dermatitis and facial oedema in consumers and hand eczema in hairdressers. Clinical manifestations of hair dye allergy can be very severe and some patients require hospitalization.

To protect consumers from the development of hair dye allergy, industry has proposed to perform an allergy alert test (also referred to as skin alert test or self test) prior to hair dyeing. An allergy alert test includes the application of a small quantity of the product on the skin before dyeing the hair and is meant as a method to assess hair dye allergy.
In 2007, an opinion on consumer self-testing for hair dye allergy has been published by the Scientific Committee on Consumer Safety (SCCS) (Appendix 1). In this opinion the SCCS has reviewed the available scientific data on the allergy alert test (the SCCS refers to 'self test' in the opinion) for hair dye allergy, and specifically refers to the possible risks and benefits for consumers. The SCCS concluded that, although self-testing may offer protection to some individuals, the use of the test as it is currently proposed by industry would lead to misleading and possible false-negative results. Furthermore, SCCS concluded that there is a potential risk that the test may induce skin sensitization to hair dye ingredients.

By order of the Ministry of Health, Welfare and Sport (VWS) and the Food and Consumer Product Safety Authority (nVWA), RIVM has evaluated the SCCS opinion on the allergy alert test. In this evaluation the perspectives of dermatologists and the Dutch Cosmetics Association (NCV, Nederlandse Cosmetica Vereniging) have been taken into account.

The aim of this document is to provide an overview of the risks and benefits of the allergy alert test and to make recommendations for further development of the test in the context of protecting the consumer from acquiring hair dye allergy.

2 Hair dye and hair dye allergy

2.1 Categories of hair colouring products

Hair colouring products can be divided into four categories:

- *Temporary colouring products*
  These products are used to temporarily revive the natural hair colour. The colour disappears in two washings.

- *Semi-permanent colouring products ('kleurspoeling')*
  The colorants in semi-permanent hair dyes attach more strongly to the hair and gradually fade in four to ten washings. Two types of semi-permanent hair colour products are available: non-oxidative and oxidative products. The latter contains hydrogen peroxide that is necessary for the development of colour.

- *Permanent oxidative hair dyes*.
  Permanent oxidative hair dyes tend to be the most popular dyes on the market today. These products are long lasting, given that the colour pigments are irreversible incorporated into the hair. Permanent oxidative hair dyes are complex mixtures that contain many different ingredients and always require an oxidation step for colouring. One important ingredient of these products is ammonia, which causes swelling of the hair fibres, thereby facilitating the uptake of all ingredients. The hair dye ingredients are colourless low-molecular-weight precursors (e.g. PPD, p-toluenediamine (PTD), p-aminophenol) and couplers (e.g. m-aminophenol, resorcinol). Prior to application, the hair dye has to be mixed with hydrogen peroxide which oxidizes the colourless precursors. After incorporation into the hair larger compounds are formed through polymerization and oxidation, resulting in pigments that are irreversibly trapped in the hair fibre.

- *Others*
  In addition to the abovementioned hair colouring methods, fashion styles continuously stimulate the development of new temporary or (semi-) permanent hair dye techniques, including all over bleach (really blonde effect), highlights (streaks of lighter colour) and lowlights (streaks of darker colour).

2.2 Use of hair dyes

Nowadays, colouring our hair is becoming common practice. Currently, 60% of the Dutch women colour their hair (NCV, 2010). Compared to some years ago, consumers now start at a younger age with colouring the hair and continue with this for a longer period. A Danish study has shown that the median age at which hair dyeing is performed for the first time is 16 years (Sosted et al., 2005). In a recent meta-analysis it has been shown that hair dye allergy is an important problem in children as well. Among the five most important allergens that caused allergic contact dermatitis in children (0-18 years) were ammonium persulfate and toluene-2,5-diamine. These two hair dye ingredients were the causative allergens in respectively 11% and 6% of the children with allergic contact dermatitis (Bonitsis et al., 2011). Besides a shift in popularity towards children, there is an increased overall use of hair dye products in all age categories. Also the number of men that colour their hair has increased: 10% of

men over 40 colour their hair and this percentage is still increasing. These trends are reflected in the sales figures: since the 1980s the number of hair care products (including hair dye products) sold in the Netherlands has significantly increased (see Figure 1). These trends are also observed in other EU-member states.

Permanent hair dyes are by far the most frequently used: figures from the Dutch Cosmetics Association (NCV) indicate that the market share of permanent hair dye products is 65% in the Netherlands (NCV, 2010).

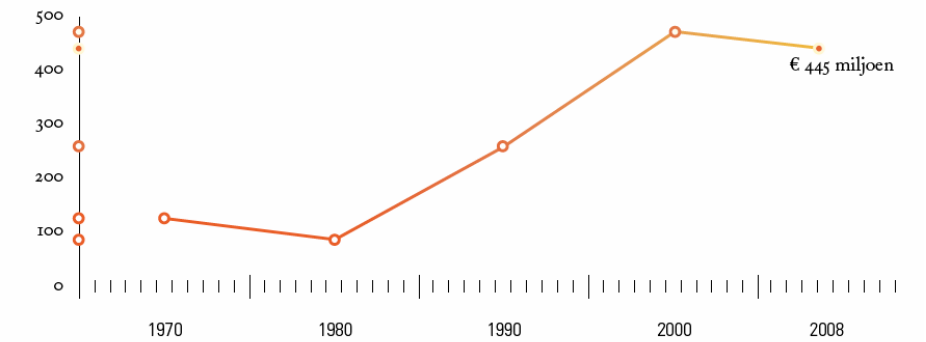

Figure 1: Sales figures of hair care products in the Netherlands (in million euros) (NCV, 2010)

2.3 Hair dye ingredients with skin sensitizing properties

Many hair dye ingredients have skin sensitizing properties and therefore the potential to induce allergic contact dermatitis ('hair dye allergy'). This is a type IV or delayed type hypersensitivity reaction, which means that it is an allergic response that is mediated by T cells. As is true for all allergies, contact dermatitis comprises two phases: an induction phase in which the immune system is sensitized and an elicitation phase in which the clinical symptoms manifest themselves upon subsequent exposures (Kimber et al., 2002).

The skin sensitizing properties of different hair dyes have been evaluated by the SCCS. They assessed the dossiers of 46 different hair dye substances and classified 27 of these hair dye substances as sensitizers. Further evaluation demonstrated that 23 of these were classified as strong or extreme sensitizers (SCCP, 2006). It is known that skin sensitizing potency is an important determinant in the acquisition of contact dermatitis. Sensitizers that are strongly potent can virtually sensitize all subjects exposed above a certain threshold level (Kimber et al., 2002).

The most well-known and most frequently studied skin sensitizer in hair dye products is PPD, which is an extremely potent skin sensitizer that has been used for more than 100 years. PPD is the only hair dye ingredient that is present in different standard series of patch tests, i.e. the European standard series (see section 2.4). Under the current EU cosmetics regulation (EC no. 1233/2009, which is a significant amendment of the Cosmetics Directive (76/768/EEC)) PPD is allowed in hair dye products with a concentration limit of 6% (calculated as free base). After mixing the product in the presence of an oxidizing agent, the on-head concentration of PPD should be at maximum 2% (calculated as free base). Although the applied concentration of PPD is usually lower than this limit (Prof Dr Coenraads, personal communication), sensitization to PPD is high among hairdressers and consumers (Guerra et al., 1992; Uter et al., 2007). PPD

is also used in semi-permanent tattoos (‘black henna tattoos’) and this type of exposure can also induce skin sensitization. Subjects that have once been exposed in this way should be cautious, since subsequent hair dyeing can elicit allergic reactions to PPD or related compounds.

2.4 Diagnosis of hair dye allergy

The diagnosis of hair dye allergy is done by dermatologists who use the patch test as a diagnostic tool to assess contact allergy. In most cases, standardized patch test systems are used which are commercially available (i.e. the European Standard Series and the True Test). For hairdressers specific hairdresser series are available that contain several sensitizing hair dyes ingredients. The principle of the test is that the substances are applied on the upper back of the patient and stay there for two days under occlusion (see Figure 2).

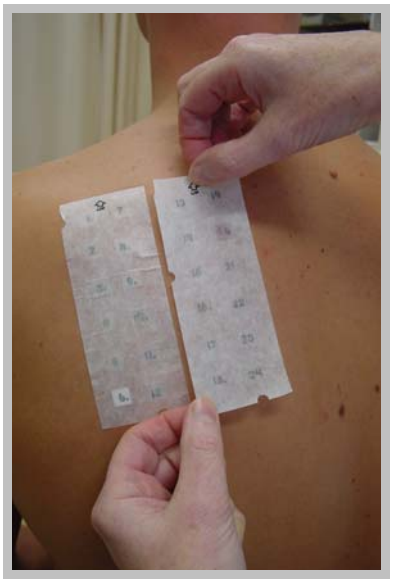

Figure 2: Application of a patch test

Skin reactions are then read by a dermatologist on the day of removal (day 2) and day 3 and sometimes day 7. Patch test reactions are scored according to international standards (ICDRG grading scale), using the following gradations: negative, doubtful (+?), weakly positive (+), moderately positive (++) and strongly positive (+++) (Wilkinson et al., 1970). Substances not present in the standard series can be tested as well, using the same protocol.
Although this test is the gold standard for diagnosing contact allergy, it has several pitfalls. In general, the results of the patch test should not be regarded as stand alone, but its relevance should be evaluated in the context of clinical history and physical examination. Specifically, testing of multiple substances at once might give rise to false-positive results. The sensitivity and specificity of the patch test is strongly dependent on the sensitizer and on the severity of patch test reactions in the patients. Patients who respond with strong skin reactions (++ or +++) will be detected more easily than those with a weak response (+? or +). In addition, the patch test reaction of substances with strong irritant properties is difficult to score because it is hard to distinguish between an irritant reaction and a skin sensitization reaction. For these substances only concentrations that do not induce skin irritation can be used and this concentration might be too low to elicit allergy reactions. It is estimated that

the overall sensitivity of the patch test is approximately 70% (Nethercott, 1990).

2.5 Prevalence of hair dye allergy

The prevalence of PPD allergy has been studied in the general population and in selected populations such as patients with contact dermatitis. The prevalence of hair dye sensitization is expressed as the percentage of subjects that responds positive in the patch test. Prevalence of allergy induced by other hair dye ingredients is not investigated in these studies.

In the general population the prevalence of PPD sensitization ranges from 0.3 to 1% for European studies. In patients with allergic contact dermatitis it was shown that during the last decades the prevalence is relatively stable. In North America 2 to 6% had a positive patch test to PPD and in Europe 4 to 7%. Patch test results from dermatitis patients from Asia show more variation: 2 to 14% were sensitized to PPD (Thyssen et al., 2009).

2.6 Severity of symptoms

The severity of clinical reactions differs largely between subjects with a PPD allergy. Some individuals are still able to dye their hair and only experience a mild rash. In others, very severe reactions can be elicited, including scalp and facial oedema which might require hospitalization. The prevalence of severe hair dye allergy is not thoroughly investigated. In a retrospective study in 400 subjects with a positive patch test to PPD it was shown that the 51% had a weak (+) patch test response, 39% had moderately positive (++) patch test responses and 10% had strongly positive (+++) patch test responses (Ho et al., 2005). These percentages were not different between hairdressers and consumers. There was a strong association between temporary henna tattoos and severe patch reactions, indicating that these henna tattoos are a risk factor for severe reactions. In this study a clear association was found between continued hair dyeing and the strength of the hair dye reactions. The majority (73%) of subjects with weak patch test responses (+) continued hair dyeing. Fifty percent of those with a moderately positive patch test response still dyed their hair, whereas none of the strongly positive patch test responders dyed their hair again (Ho et al., 2005).

3 Strategies to prevent hair dye allergy

To prevent the development of hair dye allergy or at least reduce the risk of a severe allergic reaction, several strategies can be distinguished at the governmental level and at the level of industry.

3.1 Legislation

By means of the EU-regulation on cosmetic products, the use of specific ingredients in cosmetics is regulated. This regulation contains a list of substances that are prohibited or have restrictions (concentration limits) for use in cosmetic products. Under the current regulation PPD is allowed in hair dye products with a concentration limit of 6% (calculated as free base). After mixing the product in the presence of an oxidizing agent, the on-head concentration of PPD should be at maximum 2% (calculated as free base). PTD is allowed in hair dye products with a concentration limit of 10% (calculated as free base).

This legislation is intended to protect consumers. However, in almost all cases limits are arbitrarily chosen with the purpose to help already sensitized people preventing exposure and thus avoiding elicitation. The question remains whether these limits are sufficient in practice to protect consumers from becoming sensitized.

3.2 Safety instruction on the product

Besides a clear description of the proper use of the hair dye product, hair dye products also provide safety instructions. These instructions include the warning that hair colorants can cause an allergic reaction and that especially subjects who have had a black henna tattoo before are at higher risk of developing a skin allergy. In addition, consumers are advised not to dye their hair when they have previously experienced an allergic response after the use of a hair dye product. Finally, in order to prevent the development of an allergic reaction the European Cosmetics Toiletry and Perfumery Association (COLIPA) has issued to include in the safety instructions the advice to always perform an allergy alert test 48 hours before using the hair dye product. In case an abnormal reaction, e.g. itching, redness or swelling, is noticed during the test period, the product should not be applied.

3.3 Public awareness

Besides safety instructions on the product it is important to increase public awareness on the potential risks of hair dyeing. Public awareness should encourage consumers to read the safety instructions carefully and perform hair dyeing accordingly.
Public awareness can be increased by a public health campaign which can assist the consumer in their decision to dye his/her hair or not. Also hairdressers can play a role in this. By means of a campaign, the public can be informed about (a.o.):

- the potential risks of using a hair dye;
- reasons why a consumer should be advised not to dye the hair;
- recommendations for safe use of hair dye products;
- the need to read the package leaflet carefully;
- what to do in case of an allergic reaction.

3.4 Development of new formulations

Considering that the consumer will keep the wish to dye his/her hair, the most effective measure is to change the hair dye formulation by replacing hair dye ingredients with potent skin sensitizing properties by non-sensitizing or less potent sensitizing substances. According to the Dutch Cosmetics Association (NCV), industry is working continuously on the development of new formulations that contain a lower concentration of sensitizing agents or in which sensitizers (for instance PPD) are replaced by other hair dye ingredients. However, the NCV states that it will be impossible to totally replace PPD by other ingredients because PPD is required to achieve the full range of colours the consumer wishes to have. Moreover, most of the substances that replace PPD have a similar chemical structure and, as a consequence, due to cross-reactivity these substances can also elicit allergic reactions in PPD sensitized subjects.

In the next chapter, the procedure of the consumer allergy alert test is described in greater detail. In chapter 5 the opinion of the SCCS on the test is presented. In chapter 6 the potential risks and benefits of the allergy alert test is discussed based on available peer-reviewed literature and the opinions of different stakeholders. This document concludes with recommendations for further development of the allergy alert test and suggestions for other strategies in the context of protecting consumers from acquiring hair dye allergy.

4 Consumer allergy alert test for hair dye allergy

In the safety instruction of some hair dyes it is advised to perform an allergy alert test 48 hours prior to hair dyeing. This advice is initiated by COLIPA and is aimed at preventing the development of hair dye allergy. The advice of COLIPA does not include guidance on the procedure how to perform an allergy alert test. Hence, test instructions on the package leaflet vary greatly between manufacturers.

4.1 Duration of exposure

One of the differences is the duration of exposure, which ranges from 45 minutes to 48 hours. In reality, most hair dye products are applied for 30-45 minutes. Therefore it would be more realistic to apply an allergy alert test for 30 minutes as well and not for 48 hours since this might increase the risk of active sensitization. It has been shown that application of hair dye containing 2% PPD for 30 minutes is sufficient to elicit skin reactions in all subjects with strong (++) to extreme (+++) patch test reactions to PPD. In subjects with weak (+) patch test reactions to PPD, 67% had a positive skin reaction (Goebel et al., 2010). The effects of duration of exposure were also shown in a study in which a hair dye product containing 0.5% PPD was applied for 30 minutes, 1 and 48 hours. Application for 30 minutes resulted in positive clinical skin reactions in more than 50% of the subjects with a strong (++) patch test and more than 90% (+++) of those with an extreme patch test. In the weak (+) responders, 30 or 60 minutes exposure failed to induce a skin reaction in all tested subjects (Jowsey et al., 2006). This illustrates that under realistic settings a short application of the hair dye product can predict clinical reactions in the majority of patients with strong and extreme reactions. The notion that people with a weak patch test reaction to PPD continue to dye their hair, might be explained by the fact that they respond with no or only mild clinical signs when they are exposed for only 30 minutes (Ho et al., 2005).

4.2 Application site and procedure

In contrast to diagnostic patch testing, the recommended application sites for the allergy alert test are the scalp area close to the ear or the crook of the elbows. At these sites the skin is relatively thin and therefore a sensitive location to test for hair dye allergy. From literature it is known that anatomical sites differ in sensitivity at patch testing. However, a dose-response study with PPD showed no statistical differences in response between the upper back, the lateral aspect of the upper arm and behind the ear when read by a skilled person (Aberer et al., 1993). However, the crook of the elbow may be the preferred location because consumers can easily monitor the occurrence of a sensitization reaction after application of the test. Furthermore, the skin behind the ear is less preferred, since this area is close to the scalp area that is exposed during the actual hair dyeing. Although it is currently unknown what the effect is of multiple exposures, theoretically there would be a higher risk of sensitization when the application site of the self test is close to the scalp area, since both areas drain to the same lymph nodes, possibly enhancing the risk on sensitization. Also for this reason the crook of the elbow is in the preferred site of application.
The product that is applied to the skin differs between manufacturers as well. Some procedures recommend to test the hair colour alone or to perform the test with the mixture of hair colour and hydrogen peroxide.

4.3 Accuracy of the allergy alert test recommended by industry

Two studies were found that have tested the sensitivity and specificity of an allergy alert test procedure described in the safety instructions of a hair dye product (in this case from L'Oréal). The details of these studies can be found in the SCCS opinion (Appendix 1).

In short, both studies were performed in a clinical setting and skin reactions were evaluated by an experienced dermatologist. In the first study 30 volunteers with positive patch test reactions (+, ++ or +++) to PPD and 30 volunteers who did not respond to PPD and were not familiar with a history of adverse reactions to hair dyes were included. The test product contained 1.8% PPD, and 6 other contact sensitizing hair dye ingredients. The product was applied to the skin behind the ear for 48 hours. On the first day 16/30 PPD-positive subjects and 13/30 PPD-negative subjects reacted with mild irritant reactions, low grade erythema and/or sensory manifestations. All 30 PPD-positive subjects reacted on day 2 with erythema and the dermatologist diagnosed all PPD-positive subjects correctly with the allergy alert test. In the control group, 3 subjects had mild erythema on day 2. After evaluation by a dermatologist, only one control subject was considered to be positive. This study shows that the sensitivity of the allergy alert test was 100% and the specificity 97% (Krasteva et al., 2002).

In a second study, four different products were tested in 34 PPD-positive and 49 PPD-negative subjects. The concentration of PPD in the different products was 0.1%, 0.5%, 1.0% and 1.5%. The test products were left on the skin behind the ear for 48 hours. Reactions were then evaluated by a dermatologist at day 0 (1 hour after application), day 2 and day 4. A total of 79% of the PPD-positive subjects responded to 0.1% PPD. Of the remaining 7 subjects, 3 responded to 0.5%, 3 to 1.0% and 1 to 1.5% PPD. In the control group, no reactions occurred after application of the different products (Krasteva et al., 2005). This study shows that the sensitivity of the allergy alert test depends on the concentration of PPD in the product. The majority of the patients already responded with a clinical reaction to the product with the lowest concentration. Those not responding would probably not experience any problems while using this product.

The results of both studies suggest that the allergy alert test is a sensitive tool to assess PPD allergy. One important limitation of these studies is that the complete procedure is performed in a clinical setting and that the skin reactions are evaluated by dermatologists. In real life, consumers would perform this allergy alert test at home and judge the skin reactions themselves. Both study groups were therefore not representative for the population that will perform this allergy alert test and it is unclear if this would affect the conclusion on the accuracy of the allergy alert test.

5 Summary of the SCCS opinion

The SCCS opinion on self-testing for hair dye sensitivity can be found in Appendix 1. The most important conclusions of the SCCS with respect to the allergy alert test (the SCCS refers to 'self test') as recommended by COLIPA are summarized below.

- In the studies of Krasteva et al. (2002, 2005) the allergy alert test with PPD was performed in a clinical setting and the outcome was evaluated by dermatologists. It is unclear whether the sensitivity and specificity of the allergy alert test would be the same if performed with other hair dye ingredients than with PPD. Moreover, the performance could be different when consumers apply the test and assess the outcome themselves instead of experienced dermatologists.

- Patch testing should be performed by skilled dermatologists. Reading of the skin reactions should be done on day 2, 4 and 7, since late reactions can occur. These will be missed in the recommended allergy alert test.

- The allergy alert test recommended by COLIPA is not standardized and is uncontrolled. It allows large variations in dose, duration of exposure, number of applications. False-negative and false-positive results are expected and sensitization may occur as a result of repeated application of high concentrations of hair dyes.

- False-negative outcomes are considered to be the biggest problem. Consumers expect the product to be safe when the allergy alert test is negative, but severe reactions may be elicited when the consumer dyes the hair.

6 Interviews with experts in the field

Based on the available background information on the allergy alert test and taking into account the SCCS opinion, several stakeholders were interviewed. Dr. Ir. R. van Welie of the Dutch Cosmetics Association (Nederlandse Cosmetica Vereniging, NCV) was asked to give its opinion on the risks and benefits of the alert test for hair dye allergy. Also two dermatologists, Prof. Dr. P.J. Coenraads (UMCG, Groningen) en Dr. R. Rustemeyer (VUmc, Amsterdam) were interviewed to give their personal opinion on the allergy alert test. In addition, an EU-workshop on the allergy alert test was attended.

There are several ways to address the benefits and risks of an allergy alert test for hair dye allergy. For the Ministry of Health, Welfare and Sport and the Food and Consumer Product Safety Authority, protecting consumer safety is the major reason for being interested in an allergy alert test. With this in mind, the starting point for the interviews is that an allergy alert test should have the intention to protect the consumer who wishes to colour his/her hair.

The topics that were discussed in the stakeholder interviews were:

1. How should the test be performed?
- Standardization
- What substances should be tested?
- Easy and simple
- Exposure duration

2. Validity of the test
- False-positive results (specificity)
- False-negative results (sensitivity)
- Suitable to be applied by consumers?
- Interpretation of the test results

3. Risks of the test
- False-negative results
- Induction of active sensitization
- Exposure to multiple allergens in short time

4. Other
- Role of hair dressers
- Allergy alert test in the United States
- Consumer behavior

6.1 How should the allergy alert test be performed?

6.1.1 Standardization

Currently, the hair dye products that contain the advice for an allergy alert test use non-standardized test protocols. The lack of standardization is one of the major remarks of the SCCS. Also the dermatologists, Rustemeyer and Coenraads underline the great importance of standardization of the test protocol: e.g. in terms of dose, duration of exposure, number of applications, and method of application, open or occluded and composition of the test substances. NCV agrees with the importance of standardization. Industry has just made a start with advising their customers to perform an allergy alert test, which is already a step forward according to the NCV. Because of the current lack of guidance, each manufacturer included its own test protocol in the safety instruction.
Rustemeyer would be in favour of a standardized ready-to-use test kit that is included in the hair dye package. The NCV is not aware of a hair dye

manufacturer who already provides a ready-to-use test kit with the hair dye package. To date, no discussions were held on the possibility to design a common test protocol or standardized kit, but, according to NCV, industry is willing to talk about this.

Coenraads raises the issue of performing a test *each time* the consumer wishes to dye his/her hair. An allergic reaction can develop over time, meaning that once a negative result does not necessarily mean the same outcome the next time a test is performed, especially after exposure to a hair-dye procedure. It is unknown if frequent self-testing would increase the chance of becoming sensitized.

6.1.2 Easy and simple to use

From a colleague in the UK, Rustemeyer learned about a patient who, due to unclear safety instructions, had applied an allergy alert test on his skin during more than one day, resulting in induction of sensitization. The example of the UK patient illustrates that a complicated or unclear protocol can induce a health risk. A test should be simple and easy to perform.
In Rustemeyer's opinion consumers are very well capable of reading the test outcome correctly and identify a positive result, e.g. a rash or itching. In a German study on a Danish product for self-testing for nickel and fragrance allergy the outcome of the self test evaluated by the consumer was compared to the outcome of the test performed by a dermatologist [Coenraads, unpublished data]. It was shown that there was a high concordance between both outcomes, which suggests that consumers are capable to perform and read out a patch test for these sensitizers. If this holds true for the self test for hair dye allergy, however, was not yet investigated. Coenraads indicates that the test results in the case of a hair-dye allergy may be easier to read than for a nickel or fragrance-mix allergy, which are also difficult to read in the patch tests. Coenraads is of the opinion a consumer can identify itch and/or redness at the test site (indicating that 'something is going on'). But a reliable test for hair dye allergy should be performed by a dermatologist.
In all cases, the self test should not be regarded a diagnostic tool. In case of a positive test outcome, consumers should always seek medical advice and consult a dermatologist for diagnostic patch testing.

6.1.3 What substances should be tested?

In some test protocols, the manufacturer advises the consumer to perform the test with the individual components of the hair dye. Other protocols indicate that the test should be performed with a mixture of the hair dye components. Coenraads suggests to test the hair dye in the composition in which it is finally used, meaning that the components should be mixed. A problem with this is that the mixture is instable and should be applied to the skin directly. This enforces the need to consider a separate test kit in which the components are mixed prior to skin application of the allergy alert test.

6.1.4 Exposure duration

Also the duration of the application of the allergy alert test should be in line with the final exposure, according to the consulted dermatologists. Most hair dye formulations have to be applied for 30 minutes, but some protocols advise to apply the test for 24 hours. In most protocols, the outcome of the test is evaluated after 48 hours. In addition, the shorter the exposure duration the better, in order to reduce the risk of induction of active sensitization.

6.2 Accuracy of the allergy alert test

Accuracy of the allergy alert test is, among others, described by specificity and sensitivity. Overall, the patch test has an accuracy of around 70%. Hence, it is not expected that an allergy alert test will give better results.
Considering specificity, a problem may be false-positive results, meaning a positive outcome of the allergy alert test although the consumer is not allergic. From a public health perspective, however, this is not considered to be a problem. In case of a positive test outcome, the consumer will be advised not to use the product and seek medical advice. Subsequently, a dermatologist may perform a patch test and conclude that, although the allergy alert test was found positive, the consumer can still use the hair dye product.
With respect to sensitivity, the SCCS considered false-negative results from self-testing to be the largest problem. As a consequence of this outcome, the consumer will use the hair dye product to which he/she is allergic. However, it can be questioned if false-negative outcomes will really cause harm to consumers in practice. Coenraads has performed a study on the allergy alert test for hair dyes in close collaboration with Trier University (Germany) and Procter & Gamble. This study showed that sensitivity of the allergy alert test is higher (appr. 80%) for ingredients that evoke a moderate or strong allergic reaction than for ingredients that elicit a weak reaction. Also other studies have indicated that especially the strong responders will be tested positive in an allergy alert test. The weak responders will most probably show doubtful or weak responses in this test. Rustemeyer refers to the study by Ho et al. (2005), that showed that people with a weak PPD reaction are still able to dye their hair. If false-negative reactions predominantly occur in weak responders, this may not be a major issue according to him, as these people can dye their hair without any problems.

6.3 Risks of the allergy alert test: induction of active sensitization

One possible risk associated with self-testing is that people may become sensitized to one of the ingredients. This is one of the concerns that was raised by the SCCS. The risk of active sensitization has also been an issue in the safety of patch testing using standard series. Patients with dermatitis that undergo a patch test are exposed to all sensitizers present in the standard patch test and this might lead to sensitization. Active sensitization is difficult to assess. It has been hypothesized that late reactions, i.e. those that occur seven days after exposure, are indicative for active sensitization. According to Coenraads, it is still under debate whether this holds true. The studies that have assessed active sensitization induced by PPD patch testing estimate that 0.24-1.0% of the patch tested subjects were sensitized (Devos and Van der Valk, 2001; Dawe et al., 2004; Hillen et al., 2006). In Germany, PPD has been deleted from the standard series because of the risk of active sensitisation observed from clinical data generated from a number of departments. In The Netherlands, PPD is still included in the standard series.
Coenraads is of the opinion that the risk of active sensitization should be put into perspective. In real life subjects that purchase a hair dye product are intending to dye their hair. Regardless of self-testing, they would be at risk for sensitization anyway. In that sense the risk of active sensitization is not so relevant for self-testing.

Another risk that was described to be associated with the allergy alert test is the risk of multiple exposures to one ingredient. It has been postulated that due to accumulation in skin a second exposure may evoke a more severe reaction. However, evidence for accumulation of PPD in skin is disputable, according to

the consulted dermatologists. There is poor knowledge on what happens in the skin after exposure to PPD. Nevertheless, Coenraads is not in favour of such a test because each skin test implies extra skin exposure.

6.4 Other issues: role of hairdressers

A point that is addressed by the NCV is that especially hairdressers are in the unique position to assist consumers in their decision to colour his/her hair or not. Hairdressers in salons can ask their clients if they are aware of any encountered adverse effects related to hair dyes.
In some Dutch salons, hairdressers do ask their clients about a clinical history, but, according to the NCV, this is by far not common practice yet.
Safety instructions of some professional hair dye products, such as the products from Keune, not only advise to ask the client about a clinical history but also suggest hairdressers to perform an allergy alert test 48 hours prior to the actual colouring. However, in practice such a test is rarely done. It is unpractical that a client should come to the salon two times. In contrast, in the UK it is very common to perform an allergy alert test (source: COLIPA).
According to the NCV hairdressers should actively encourage their clients to perform an allergy alert test.

6.5 EU-Workshop on the allergy alert test

On 6 April 2011 a workshop was organized by DG Sanco about the allergy alert test to assess hair dye allergy. In this workshop representatives from industry (COLIPA) and field experts (dermatologists and scientists) from different EU-member states participated. Joanne Salverda-Nijhof also participated in this workshop and gave an introductory presentation on the allergy alert test and its potential risks and benefits.
During this workshop, industry underlined that they are working on finding new substitutes to replace potent skin sensitizers in hair dyes (e.g. PPD), but to date no satisfying candidate has been found. Also the risks and benefits of the allergy alert test in its current form were discussed. Experts underlined the need to standardize the test procedure. Moreover, several data gaps were identified among which the lack of knowledge whether consumers are able to adequately perform and evaluate the allergy alert test. Based on the concerns and identified data gaps from field experts, a list of issues was derived that needs to be further addressed by industry. Industry proposed to set up a new study to investigate whether consumers can adequately perform an allergy alert test. In this context, industry is prepared to work together with field experts.

6.6 Summary

- Rustemeyer is in favour of an allergy alert test, but only if the test protocol is standardized (see section 6.1).
- Coenraads has doubts about the usefulness of a self test. Maybe a few cases of hair-dye reaction can be prevented, but this should be weighed against the fact that each test implies extra skin exposure. Moreover, he is of the opinion that a reliable reading of a patch test should be performed in a clinical setting performed by a dermatologist. And he questions whether consumers will have the patience to wait for the 48 hour outcome?
- NCV is of the opinion that consumers should always perform a test each time the consumer wishes to use a hair dye product. Especially people with a strong allergic response will benefit from this test.
- Industry is prepared to discuss the issue of standardization of self-testing and is intended to study further whether consumers are able to adequately perform an allergy alert test.

7 Conclusions and recommendations

Based on available peer-reviewed literature, the opinion of the SCCS, the interviews with different stakeholders and the EU-workshop, the authors of this report conclude that the allergy alert test is appreciated as a valuable tool to assess if the hair dye product could elicit an allergic skin reaction. The test would then function as an alert to undertake further steps, including a medical consultation with a dermatologist.
However, in the authors' opinion the allergy alert test in its current form should not be recommended. Further development of the allergy alert test is necessary. Specifically, it is important to address the issue of standardization in terms of exposure duration, application site and test formulation. Preferably, the test procedure should be similar to the actual use of the hair dye product, meaning that the exposure duration should be at maximum 30-45 minutes and the final product formulation should be tested. To make it easier for consumers to monitor reactions, the allergy alert test should be applied at the crook of the elbow. For the development of the allergy alert test it is recommended to work together with industry. Furthermore, it is the authors' opinion that industry should further investigate whether consumers are able to adequately perform and evaluate the allergy alert test.

In addition to the further development of the allergy alert test, it is recommended to launch a campaign to create more awareness under consumers and hairdressers. A study performed by Ifop (Institut français d'opinion publique) in several EU-countries has shown that awareness is essential for compliance of the allergy alert test. Lack of awareness reduces the motivation of consumers and hairdressers to perform an allergy alert test (data obtained from COLIPA). The campaign should inform about the potential risks of hair dyes. It is important that people also become more aware of the risk factors for the development of hair dye allergy such as a henna tattoo and a previous encountered problem after a hair dye treatment. In case of an adverse reaction, people need to know that they should seek medical attention and visit a dermatologist.

It is important that industry informs relevant stakeholders (e.g. policy makers, dermatologists) about new product developments and the progress they have made with product formulations that contain new non-sensitizing ingredients. Furthermore, an approach to reduce the burden of hair dye allergy is to estimate acceptable exposure levels to sensitizing hair dye ingredients. These levels should be below the threshold for the induction of skin sensitization. In this way the risk of becoming sensitized to hair dye ingredients would be minimal. It is therefore recommended to perform a quantitative risk assessment (QRA), similar to the one done with fragrances by the Research Institute for Fragrance Materials (RIFM) (Api and Vey, 2008), enabling the estimation of safe levels in hair dye products.

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Appendix 1: SCCP opinion

Scientific Committee on Consumer Products

SCCP

OPINION ON

Sensitivity to Hair Dyes - Consumer Self Testing

The SCCP adopted this opinion at its 14th plenary meeting on 18 December 2007

About the Scientific Committees
Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Evaluation Agency (EMEA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCP
Questions concerning the safety of consumer products (non-food products intended for the consumer).
In particular, the Committee addresses questions related to the safety and allergenic properties of cosmetic products and ingredients with respect to their impact on consumer health, toys, textiles, clothing, personal care products, domestic products such as detergents and consumer services such as tattooing.

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1. BACKGROUND

Some hair dyeing products placed on the Community market contain the advice to assess skin sensitisation by performing a user test before dyeing the hair ("**self tests**"). To this end, the labelling advises to apply a small quantity of the hair dye on the skin.

COLIPA[1], in a "recommendation" on "Warnings on oxidising hair colouring product for consumer use" recommends a leaflet with the following 'safety instructions': "Perform a skin allergy test 48 hours before each product use" (full text of the recommended safety instruction in Annex I).

Some Member States have concerns and point at possible risks stemming from self tests.

The Cosmetics Directive does not contain an obligation for manufacturers/importers to provide for self-tests. Rather, Commission Directive 92/86/EEC of 21 October 1992 *lifted* the obligation to label the warning "sensitivity test advisable before use" for certain hair dyes[2].

This was a consequence of opinion SPC/54/92 of the Scientific Committee of Cosmetology (SCC) concerning current requirements for requesting user test for allergy before use of some hair dyes of 10 February 1992.

In this opinion, the SCC stated the following:

- Sensitivity testing "*should be performed by adequately trained dermatologists who will be medico-legally responsible for any problems related to false negative results and active sensitisation, and who are trained to evaluate any response and can give advice accordingly* "(p. 3)

- In particular, there is the risk that the consumer uses an "*unstandardised amount of dye to an unstandardised area of skin and that there is no occlusion*". As a consequence, "*although some PPD[3] allergic individuals will develop an easily observable reaction, an unknown number of individuals who are PPD[3] hair dye allergic will develop no reaction i. e. a false negative result, and some will be actively sensitised by the procedure*" (p. 4)

- The SCC concluded that "*the 'sensitivity testing' procedures suggested by manufacturers have to be considered as diagnostic tests. There is no published evidence of how helpful such non-standardised tests are in detecting PPD[3] sensitivity. There are numerous anecdotal reports of individuals who claim to have been tested with a hair dye as recommended by manufactures but who develop an allergic contact reaction when their hair is dyed. There are medico-legal implications in suggesting a test with an unknown sensitivity for detection and with poor standardisation. Further, such tests may be performed before a first hair dye, when allergy to PPD should not be present (no previous exposure) but not before subsequent colourings when allergy may have been acquired (because of ignorance)*" (p. 4)

However, since 1992, different views have been voiced on this issue. It has also been argued that self-test are beneficial to the consumer as they provide for a pre-screening of sensitisation (which may be followed-up by patch testing by a professional).

[1] COLIPA - European Cosmetics Toiletry and Perfumery Association
[2] Substances with reference numbers 8, 9 and 10 of Annex III
[3] p-Phenylenediamine

Therefore, the Commission deems it necessary to seek clarification from the Scientific Committee on Consumer Products (SCCP) on the risks and benefits of self-tests.

2. TERMS OF REFERENCE

In the light of the data available,

1. *Does the SCCP consider that there is a risk that:*
   - *Self-tests lead to false-negative results?*
   - *Self-tests lead to induction of contact allergy?*
2. *Does the SCCP consider that self-tests are beneficial for a specific population of hair dye users in order to detect existing sensitisations?*

3. ASSESSMENT

3.1. Introduction

Contact allergy and allergic contact dermatitis caused by hair dyes is an important and increasing health problem to consumers, hairdressers and society. Hair dyes are causing acute and severe dermatitis on the face, scalp and neck in consumers, and hand eczema in hairdressers. Several studies in Europe and in Asia show that contact allergy to p-phenylenediamine (PPD) has increased significantly in the general population, in dermatitis patients, and in hairdressers over the last decades (13, 14, 18, 25, 28). Positive patch test reactions to PPD were found in 3% of dermatitis patients in Europe and North America (4), in 4.8% of dermatitis patients in Germany (8), in 2.3% of the general population in Thailand (3), in 22% of hairdressers (dermatitis patients) in Germany (25) and 37% in Italy (9), and in 6% of hairdressers (non-patients) in the Netherlands (26).

The SCCP and the former SCCNFP have recently assessed the dossiers of 46 of the 117 hair dye substances of interest to industry regarding their skin sensitising property. In a memorandum on hair dye substances and their skin sensitising properties, based on adopted opinions on these 46 hair dye substances, 10 were categorised as extreme, 13 as strong and 4 as moderate skin sensitisers, all fulfilling the EU criteria for classification as a skin sensitiser (R43) (19).

Among the extremely potent skin sensitisers are PPD and related compounds that have been used for more than 100 years. More than two thirds of hair dyes currently used contain PPD. Other examples of much used hair dyes, known to be strong or extreme skin sensitisers, are Toluene-2,5-diamine (TDA), 4-Amino-2-hydroxytoluene, and p-Aminophenol (19, 21).

3.1.1. Diagnostic patch testing

Diagnostic patch testing is the procedure used for detection of contact allergy to substances. The test procedure is standardised with regard to test substances (European standard series, and other series), concentrations and vehicles, amount of test substance applied, test systems (occlusion), application site (upper back), application time (2 days), reading time (recommended on approximately 2, 4 and 7 days after application), and

grading scale for assessment of test reactions. When substances outside the standard series are tested, special care has to be taken not to cause harm to the patient by inducing allergy, irritation, scarring, pigmentation or other local effects, systemic effects, or by false-negative test results. Patch testing requires experience and should be performed by dermatologists with adequate training. (2, 12, 27)

The only hair dye substance in the European standard series for patch testing is PPD (at 1% in petrolatum). The preferred test concentration has varied over time and between authors, considering the risk of inducing allergy by patch testing versus the risk of false-negative result. The concentration has been lowered in some clinics (1), while other experts recommend that the current 1% PPD should be kept (7, 15). PPD has recently been deleted from the standard series in Germany because of the risk of active sensitisation observed from clinical data generated from a number of departments (20), however, active sensitisation has not been considered to be a problem elsewhere (6, 7, 24).

3.1.2. "Self test" in relation to medicinal products

The Danish Medicines Agency has determined that the product "Colourstart" is a medicinal product according to section 2, n° 2 in the Danish Medicinal Products Act (5), as the product is meant to make a medical diagnosis. The decision for this was that "Colourstart" is a patch testing preparation containing PPD and intended for the purpose of identifying individuals who have an allergy to PPD. "Colourstart" is marketed to hairdressing salons in order to make it possible for the hairdresser to test people before permanent hair colour treatment. According to the Danish Medicinal Products Act, medicinal products must not be manufactured, imported, exported, stored, sold, supplied, dispensed or packed without authorisation from the Danish Medicines Agency, and no medicinal product may be distributed unless a marketing authorisation has been granted by the Danish Medicines Agency or granted according to regulation laid down by the Council of the European Union.

In a note on the question whether and under what circumstances allergy self-tests for hair dyeing products are medicinal products, it was stated by DG Enterprise and Industry, Consumer Goods, Pharmaceuticals (ENTR F/2), that devices for allergy self testing fall under the pharmaceutical legislation as defined in Directive 2001/83/EC, and that a product intended for the diagnosis of allergic reactions is to be authorised according to Directive 2001/83/EC (16).

In a second note on the question of whether hair dyeing products and related testing kits are to be classified as medicinal products, the view of DG Enterprise and Industry, Consumer Goods, Pharmaceuticals (ENTR F/2) was summarised (17):

1. Hair dye products with safety instructions including advice to test the product beforehand are not medicinal products, as they are presented as intended for hair dyeing and the function is to dye the hair.
2. Autonomous testing devices in order to assess the sensitivity to some components of hair dye fall under the pharmaceutical legislation as defined in Directive 2001/83/EC as they are devices for allergy self testing with the purpose to establish a diagnosis.
3. In kits containing hair dye and an additional testing device, the separate testing device is considered as a medicinal product, while the hair dye is not a medicinal product.

3.2. "Self test" recommended by industry

In a submission by COLIPA, it is stated that: "Some differences exist in the methodology recommended by individual hair colorant manufacturers. Recommended application sites include the scalp area close to the ear or the fold of the elbow. Some manufacturers

recommend application of the neat hair colorant or after mixing with hydrogen peroxide. The product may be rinsed after 45 minutes or left on the application site for 48 hours. These somewhat different methodologies reflect different regulatory requirements by non-European authorities specifying different test conditions." Examples of "self test" instructions by industry are given below.

> *"Carry out a sensitivity test 48 hours before the use of this product, even if you have previously used a hair colour product from this brand or any other brand.*
> *Sensitivity test: With surgical spirit clean an area of 1 cm^2 behind your ear and apply a small amount of the Nourishing Colour Cream contained in tube B with a cotton tip to the cleaned area; reapply 2 or 3 times and let dry in between. Carefully close the colorant tube again. Wait for 48 hours without washing. If during this period you notice itching or reddening do not use this product.*
> *In the case of an intense tingling sensation, a rash, or a burning sensation on the scalp rinse immediately with lukewarm water and discontinue use. Before attempting to use a hair colour product again consult your doctor." (Garnier Nutrisse)*

> *"Conduct a skin allergy test 48 hours before each product use even if you have already used colouring products before. This should be done like this:*
> *Sensitivity test: Perform the skin test on an area of skin sized approximately 1 cm x 1 cm on the inside of the elbow. Apply a small amount of the colour gel in a thin layer on the inside of the elbow with a cotton bud and leave uncovered for 45 minutes. Avoid contact with clothes. Close bottle again carefully. After 45 minutes, wash off the colour gel carefully with lukewarm water. If any reaction occurs during the processing time or during the following 48 hours, you should rinse immediately and not use this colorant.*
> *The absence of reaction to this test is no guarantee that an allergic reaction may not occur as a result of a future hair colouring process. However, this test is an important precaution. Please consult a doctor, if you have any doubts." (Schwarzkopf)*

Comments
The examples of "self test" instructions show that the procedure allows for large variation of crucial factors that are carefully standardised in clinical diagnostic patch testing.

1. The amount of substance applied is described as "a small amount" by 1, 2, or 3 applications.
2. The application time varies from 45 minutes to 48 hours.
3. The concentration of hair dye substance is not known, as the product is tested 'as is'. This may give up to 6% PPD or 10% TDA, the highest allowed concentration of some of the most potent skin sensitisers. Such exposure may induce sensitisation. The concentration may also be much lower than what is known to be relevant in patch testing, and the result may be false negative.
4. The reading time is up to 48 hours. This is known to be too short as patch test reactions may develop up to 7 days after application, and allergy may be missed.
5. It is difficult to understand how the test can be performed behind the ear (retro auricular area), by repeated application onto a 1 cm^2 area and how the reaction other than itching can be assessed by the subject.
6. The application site is either behind the ear or on the arm, while patch testing is done on the upper back for good reproducibility.
7. The application is open, while clinical diagnostic patch testing is performed by occluded application.
8. In clinical diagnostic patch testing, readings are undertaken by trained observers.

Summary
The "self test" gives extremely large and uncontrolled variation in dose, duration of exposure and other factors crucial for the outcome. The validity as a relevant test for contact allergy to hair dye substances is considered very low by the SCCP.

3.3. Human tests

Open tests with hair dyes

The following two experiments describe open testing of hair dye products but performed in a clinical setting.

Method:	Single open application
Subjects:	30 subjects (2 males and 28 females) with positive patch test reaction to PPD at routine investigation. 5 subjects were hairdressers. Allergy to other para-substituted derivatives was established (p-toluenediamine (n=12), disperse orange 3 (n=3), o-nitro-p-phenylenediamine (n=2)) 36 control subjects with a negative patch test to PPD and no history of adverse reactions to hair dyes.
Test product:	a marketed hair colorant containing 1.8% PPD and 6 other hair dye molecules at total concentration below 2% (2,4-Diaminophenoxyethanol HCl, Resorcinol, m-Aminophenol, o-Aminophenol, Hydroxybenzomorpholine, p-Aminophenol), matrix: water, surfactants (<30%), conditioning agents (<5%), alkalizing agents(<3%), antioxidants and stabilizers (<2%), perfume (0.5%)
Dosages:	0.1 ml applied by micropipette and combitips, spread manually over a surface of 1.75 cm^2, actual volume applied: approx. 0.085 ml

The retro-auricular area was wiped with alcohol. Circular adhesive devices (3M) were applied behind each ear. The test product was applied in the centre of one adhesive, the other was left empty as negative control. The adhesives were removed 1 hour after application, the test sites were marked. The test product was left for 48 hours without washing. Reactions were recorded on Day 0 (1 hour after application), Day 2 and Day 4. Recording was made by a scoring method evaluating the "overall clinical impression" as the severity of reaction (five-point grading scale according to Johansen et al. 1997); and by evaluation of parameters including area, erythema, papules/infiltration/oedema, vesicles/erosion, sensory manifestations (maximal total score 19).

Results
16/30 PPD-positive subjects and 13/30 PPD-negative subjects reacted on Day 0 with mild irritant reaction, low grade erythema and/or sensory manifestations. All 30 PPD-positive subjects reacted on Day 2 with erythema and infiltration. In 25/30 vesicles were observed. Sensory manifestations were recorded in 27/30. The reactions in 4/30 were evaluated with the maximal score (19/19). The reactions were evaluated as allergic. Maximal intensity of reactions was recorded on Day 2 in all but 2 subjects. The severity of reactions was reduced in most PPD-positive subjects on Day 4. 3/36 control subjects had mild erythematous reactions on Day 2.

Ref.: 11

Method:	Single open application
Subjects:	34 subjects (1 male and 33 females) with positive patch test reaction to PPD (+ to +++) at routine investigation in the last five years. 50 control subjects with a negative patch test to PPD and related allergens and no history of adverse reactions to hair dyes.
Test substances:	Product A: 0.1% PPD and other ingredients Product B: 0.5% PPD and other ingredients Product C: 1.0% PPD and other ingredients Product D: 1.5% PPD and other ingredients

	A, B, C, D contained ingredients such as resorcinol, m-Aminophenol, 2,4-Diaminophenoxyethanol ranging from 0.1% (A) to 1.64% (D) Control product Y: corresponding to A and B, without PPD or other colorant Control product Z: corresponding to C and D, without PPD or other colorant Matrices: water, surfactants (max. 30%), antioxidants, stabilisers (max 1%), perfume (max 0.5%)
Dosages:	0.1 ml applied by micropipette and combitips, spread over a surface of 1.75 cm^2 enclosed by adhesive devise. Actual volume applied: approx. 0.08 ml.

The PPD-positive subjects were tested consecutively with rising concentrations (A through D) and the corresponding control product, and a rest period of 3 to 6 weeks between two consecutive applications. When test products produced a definite allergic reaction (at least erythema with papules or homogenous infiltration/oedema) the subject was classified as SAT-positive (skin allergy test positive) and testing with products containing higher concentrations of PPD was discontinued. The PPD-negative control subjects were designated to testing with one of the products A-D respectively, and with the corresponding control product Y or Z.

The test product and the corresponding control product were applied after placing circular adhesive devices (3M) behind each ear. The adhesives were removed 1 hour after application. The test products were left for 48 hours without washing. Reactions were recorded on Day 0 (1 hour after application), Day 2 (48 ± 2 hours) and Day 4 (96 ± 2 hours). Recording was made by a scoring method including global evaluation of the severity of reaction (five-point grading scale according to Johansen et al. 1997); and by evaluation of parameters including area, erythema, papules/infiltration/oedema, vesicles/erosion, sensory manifestations (maximal total score 19). On day 2, the subjects were requested to report the earliest manifestations they had noted and the time of onset.

Results
27/34 PPD-positive subjects developed positive reaction when tested with product A (containing 0.1% PPD); 3/7 were positive to product B (containing 0.5% PPD); 3/5 were positive to product C (containing 1% PPD); and 1/1 was positive to product D (containing 1.5% PPD). Thus, all 34 PPD-positive subjects reacted positively to PPD-containing products tested.

Apart from one exception, no reaction was graded as positive in PPD-positive or PPD-negative control subjects to control product Y or in PPD-negative control subjects to product A, although several test sites showed low grade erythema which had remained unnoticed by the subjects. All reactions in PPD-negative control subjects tested with B, C or D and corresponding control product were graded negative. A PPD-negative control subject who reacted positively to product A and to the corresponding control Y was found positive to sodium metabisulfite present in A and B, and the subject was excluded from the control group.

The mean severity of reactions (overall clinical impression) to products A-D was strongest on Day 2. The test reactions were generally strong, 27/34 having vesicular reactions. All subjects reported that they had noticed a reaction, pruritus was the first symptom reported by 33/34.

Ref.: 10

Comment
The composition of the test products (A, B, C and D) and the control products (Y and Z) was not specified. The testing was not blind. The test products contained PPD. It is not possible to draw the conclusion that the sensitivity and specificity of the test would be the same, if

performed with other hair dye substances. It is not possible to draw conclusions concerning the performance if the test products are applied and reactions assessed by consumers themselves.

3.4. Discussion

Among dermatologists experienced in contact allergy and clinical diagnostic patch testing, it is well-known and generally agreed that:

- single occupational or non-occupational, open or occluded, exposure to some substances may induce sensitisation;
- patch testing may induce sensitisation to some substances;
- patch test reactions may become positive up to a week after application of the test substance; that it may be difficult to assess reactions to substances beyond the standard series; and that
- care must be taken when testing with substances and products beyond the standard series, due to the risk of causing harm to the patient by sensitisation, irritation, or false positive or false negative results.

These difficulties and concerns are the background to the general recommendation that patch testing (selecting substances for testing, preparing the patch test substances, applying the test, reading and interpreting the result) should be performed by skilled persons. Reading of test reactions should be performed on approximately Day 2, 4 and 7.
Ref.: 2, 12, 27

It is known that different anatomical sites have different sensitivity at patch testing, and the upper back is recommended due to best reproducibility and least false-negatives (27). In a dose-response study with PPD, however, no statistical difference in response was found between the upper back, lateral aspect of the upper arm and behind the ear when read by a skilled observer (22).

The "self test" recommended by COLIPA is not standardised and it is uncontrolled. It allows for very large variations in dose, number of applications, duration of exposure, etc. False-negative, but also false-positive results are expected, and sensitisation may occur as a result of repeated application of high concentrations of hair dyes which are potent skin sensitisers.

False negative results from "self testing" is considered to be the largest problem. False-negative results may cause harm to consumers, as they may lead to severe clinical reactions due to hair dyeing with substances to which the consumer is allergic.

There is a wide range of hair dye formulations. They contain different hair dye substances at different concentration and in combination with other substances, constituting individual hair dye products. The composition, including product matrix and presence of other chemicals, may affect the response at open or closed testing with hair dye products. Thus, it is not possible to extrapolate results from testing with a particular product to all other possible formulations.

The SCCP agrees with the statements in the opinion SPC/54/92 of the Scientific Committee of Cosmetology (SCC) of 10 February 1992 (23).

3.5. Comments received during the public consultation

During the public consultation, 11 contributions were received from member state authorities (2), professional and industrial associations (4), individual companies (1), consumer organisations (1), and academic individuals (3).

Some of the contributions were out of the scope of the scientific opinion requested from the SCCP, since they touched on risk management questions rather than risk assessment issues. Of the more relevant documents submitted, contributors from member state authorities, consumer organisation and academic research generally agreed with the reasoning of the SCCP and endorsed the conclusions drawn from in this opinion, while Industry associations did support the consumer patch test as currently used. After careful consideration of the contribution, the SCCP came to the conclusion that the submitted material did not provide significant new information which would lead to a change of its conclusions presented in the preliminary opinion.

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4. CONCLUSION

When a hair dye product is applied to the skin for the purpose of providing an indication as to whether the individual consumer may or may not have contact allergy to hair dye chemicals(s), the product is being used for *in vivo* diagnostic purposes.

In response to the questions asked, the SCCP is of the opinion that:

- There is a risk that "self tests" with hair dye products and with separate kits lead to misleading and false-negative results, thus giving individuals who are allergic to hair dye substances the false impression that they are not allergic or not at risk of developing an allergic reaction by dyeing their hair.
- There is potential risk that "self tests" result in induction of skin sensitisation to hair dye substances.
- Self testing may offer protection to those individuals who perform the recommended test and develop a positive reaction. However, the proportion of hair dye chemical allergic individuals who do produce a positive reaction from this *in vivo* diagnostic test is unknown.

The SCCP wishes to point out that the use of hair dye products on the skin and for *in vivo* diagnostic purposes is not covered by the current Cosmetics Directive.

5. MINORITY OPINION

Not applicable

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Annex I
Wording recommended by COLIPA for leaflet accompanying hair dyeing products according to "Recommendation to Members n° 17A "warnings on oxidising hair colouring products for consumer use"

LEAFLET

CAUTION:
Can cause an allergic reaction.
Avoid contacts with eyes. Rinse immediately if product comes into contact with them. Do not use to dye eyelashes or eyebrows. Rinse hair well after application. Wear suitable gloves.
Keep out of reach of children.

IMPORTANT: Hair colorants can cause allergic reactions which in rare instances can be severe. Tattoos may increase your risk of allergy. To reduce your risk follow these instructions.

SAFETY INSTRUCTIONS

1. DO NOT USE THE PRODUCT AT ALL IF:
- you have already experienced any reaction to colouring products.
- you have sensitive, irritated or damaged scalp.
In these cases consult a doctor before using any hair colour product.

2. PERFORM A SKIN ALLERGY TEST 48 HOURS BEFORE EACH PRODUCT USE even if you have already used colouring products before.

(Test protocol to be decided by each producer as well as the use of the following sentence:The absence of reaction to this test is no guarantee that an allergic reaction may not occur as a result of future hair colouring process. However, this test represents an important precaution. Please consult a doctor, if you have any doubts).

3. IF DURING COLOURING YOU EXPERIENCE
- any stinging or burning and/or rash, rinse immediately and discontinue use as this may be an indication of more serious reaction. DO NOT colour your hair again before consulting a doctor or seeking medical advice.
- rapidly spreading skin rash, dizziness or faintness, shortness of breath and/or swelling to eyes/face, rinse immediately and SEEK IMMEDIATE MEDICAL ATTENTION.

4. IF AFTER COLOURING OR ON THE FOLLOWING DAYS YOU EXPERIENCE problems such as skin or scalp itching, skin or scalp rash, swelling to eyes/face, blistering and/or skin or scalp weeping SEEK IMMEDIATE MEDICAL ATTENTION.

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