Environment International 89–90 (2016) 222–227

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Review Article

# The use of personal hair dye and its implications for human health

Ki-Hyun Kim [a,*], Ehsanul Kabir [b], Shamin Ara Jahan [c]

[a] Department of Civil and Environmental Engineering, Hanyang University, Seoul 04763, Republic of Korea
[b] Department of Farm, Power, and Machinery, Bangladesh Agricultural University, Mymensingh, Bangladesh
[c] BRAC Clinic, Dhaka, Bangladesh

ARTICLE INFO

*Article history:*
Received 27 November 2015
Received in revised form 24 January 2016
Accepted 24 January 2016
Available online xxxx

*Keywords:*
Hair dye
Toxicants
Health effects
Regulation guidelines

ABSTRACT

Hair dye products now represent one of the most rapidly growing beauty and personal care industries as both men and women commonly change hair color to enhance youth and beauty and to follow fashion trends. Irrespective of economic and education status, people dye their hair to emphasize the importance given to appearance. Despite adverse reactions, many people continue dyeing mainly for cosmetic purposes. This paper provides a comprehensive review on various aspects of hair dying products, especially with respect to the hair-coloring process, classification, chemical ingredients, possible human health impacts, and regulations. Permanent hair dye, which is the most commonly used product type, is formed by an oxidative process involving arylamines to bring about concerns with long-term exposure. Hence, significant efforts have been put to understand the possible side effects of such exposure including cancer risk. However, hair dyes and their ingredients are mainly identified to have moderate to low acute toxicity such as the cause of allergic contact dermatitis. Although some hair dye components are reported to be carcinogenic in animals, such evidence is not consistent enough in the case of human studies. Consequently, further research is desirable to critically address the significance of this issue, especially with respect to the safety of hair dye ingredients.

© 2016 Elsevier Ltd. All rights reserved.

**Contents**

1. Introduction . . . 222
2. Types of hair dye . . . 223
3. Toxic and/or hazardous components of hair dye . . . 223
   3.1. p-Phenylenediamine (PPD) . . . 224
   3.2. toluene-2,5-diamine (PTD) . . . 224
4. Adverse health effects . . . 225
   4.1. Skin irritation and allergy . . . 225
   4.2. Cancer . . . 226
5. Regulations . . . 226
6. Conclusion . . . 226
Acknowledgment . . . 227
References . . . 227

## 1. Introduction

Hair is an indicator of attractiveness, femininity, masculinity, health, and beauty. As society focuses more and more on youthfulness and beauty, hair dyeing has become popular among both men and women pursuing such value or fashion trends. Globally, hair colorants are a rapidly growing industry of over $7 billion (The Economist, 2015). Hair dyeing involves treatment of the hair with various natural and/or artificial chemical compounds mainly for cosmetic purposes (e.g., to cover gray hair, to change to a color regarded as more fashionable or desirable at a given time, etc.).

The association between hair dye application and the development of cancer has been a topic of debate over the past several decades. Hair dyes come in two forms: (i) oxidative (permanent) and (ii) non-oxidative (semi-permanent and temporary) (USFDA, 2014). Permanent

* Corresponding author.
*E-mail address:* kkim61@hanyang.ac.kr (K.-H. Kim).

http://dx.doi.org/10.1016/j.envint.2016.01.018
0160-4120/© 2016 Elsevier Ltd. All rights reserved.

dyes consist of primary intermediates (e.g., p-phenylenediamines (PPDs) and p-aminophenols) and couplers (e.g., m-aminophenols and m-hydroxyphenols) in the presence of peroxide (USFDA, 2014). Non-oxidative hair dyes include colored compounds that stain hair directly. Some of the chemicals used in hair dye products are reported to be carcinogenic in animals (Bolt and Golka, 2007). Likewise, the International Agency for Research on Cancer (IARC) reported that some of the chemicals in hair dye are probably carcinogenic to those who are exposed to them occupationally (e.g., hairdressers and barbers). However, hair dye products have not yet been classified as carcinogenic for personal users (IARC, 2010).

Given the widespread use of hair dye products around the globe, scientists have tried to determine the association between hair coloring products with health risk. In this review article, we provide a critical assessment of this issue by exploring the impact of hair dye on human health. This effort will help to gain better knowledge regarding contradictory or controversial myths about the use of hair dye and its possible cancer risk. To this end, the available data for meta-analytic studies for bladder, hematological, breast, skin, ovarian, and cervical malignancies have been evaluated on a parallel basis. Based on this review, we aim to provide up-to-date knowledge on the use of hair dye products and their possible impact on human health.

## 2. Types of hair dye

Graying of the scalp hair is an inevitable physiologic process with human aging. The cause of this process has been ascribed to the loss of pigment-forming melanocytes from the hair follicles, which reflects a loss of the melanocyte stem cell population in aging hair follicles (Kim et al., 2012). Coloring agents can be used to remove natural color and/or add new color. The three most common classifications of artificial hair color are permanent, semi-permanent, and temporary (USFDA, 2014).

Hair is made up of the root and shaft. The shaft has three layers; the cuticle consisting of tightly packed colorless cells, the cortex containing natural color pigments that determine color, and the medulla as a hollow core. The larger molecules of temporary hair dyes are unable to penetrate into the cortex; on the other hand, the smaller molecules of semi-permanent hair dyes easily penetrate into the cortex but diffuse out easily in subsequent washes (Madnani and Khan, 2013). In the case of permanent hair dye, the smaller dye precursors penetrate into the cortex and undergo oxidation to form large colored molecules that tend to remain within the cortex with the least possibility of diffusion (Lewis et al., 2013). Permanent hair dyes are not easily removable by shampooing. In contrast, temporary dyes are easily washed out in one shampoo rinse, while semi-permanent dyes are removed in 4 to 12 shampoos (USFDA, 2014). Temporary and semi-permanent products are direct dyes relying on van der Waals forces for adhesion; hence, they do not require chemical reactions to impart color (USFDA, 2013). Permanent dyes are actually colorless precursors and contain hydrogen peroxide (as oxidizing agents) and ammonia (as alkaline) (NCI, 2014). The depth of penetration between different types of hair dye is shown in Fig. 1.

The combination of oxidizing and alkaline agents causes swelling of the hair cuticle. Swelling facilitates diffusion of the colorless precursor into the hair cortex, which bleaches the natural melanin pigment. Eventually, oxidation of the colorless precursor proceeds into large colored molecules to be trapped inside the hair cortex (USFDA, 2013). However, the hair shaft can sustain oxidative damage with permanent hair dye use. The damage is accentuated with the use of dark-colored dyes (e.g., black and dark-brown) because darker shades need higher concentrations of precursors (Bonefeld et al., 2010). The destructive nature of permanent hair dyes, especially dark-colored dyes, is reflected in the epidemiological evidence, demonstrating its potential association to human malignancy.

On the other hand, semi-permanent hair color contains an alkaline agent other than ammonia (e.g., ethanolamine and sodium carbonate) with a reduced level of hydrogen peroxide (relative to permanent hair color) (NCI, 2014). The alkaline agents employed in semi-permanent colors are less effective in removing the natural pigment of hair than ammonia; hence, semi-permanent colors cause less damage than the permanent counterpart. Semi-permanent hair color only partially penetrates the hair shaft and thus is washed out after shampooing several times (Madnani and Khan, 2013). Semi-permanents lack or contain very low levels of developer, peroxide, or ammonia; therefore, they should be less harmful to damaged or fragile hair. Temporary hair color is available in various forms including rinses, shampoos, gels, sprays, and foams, and it is commonly used to color hair for special occasions (e.g., costume parties or Halloween). The pigment molecules in temporary hair color are large, do not penetrate the cuticle layer, and are easily removed with a single shampooing (USFDA, 2013). Temporary hair color can nonetheless persist on hair that is excessively dry or damaged in a way that allows migration of the pigment to the interior of the hair shaft (Madnani and Khan, 2013). Table 1 lists ingredients generally used in modern hair dye formulations.

## 3. Toxic and/or hazardous components of hair dye

The two main chemical ingredients involved in the hair coloring process that helps color last longer than 12 shampoos are (1) hydrogen peroxide (also known as the developer) and (2) ammonia (Lewis et al., 2013). The former is known to initiate the color-forming process to create longer-lasting color. Increased developer concentration increases the amount of sulfur that is removed from the hair, causing hardening of the hair (Helaskoski et al., 2014). This is why, for the majority of hair coloring, the developer is maintained at a 30% volume or less. However, ammonia can facilitate the lightening of hair by acting as a catalyst when the permanent hair color comes together with peroxide (Helaskoski et al., 2014). Like all alkalines, ammonia tends to separate the cuticle to facilitate the penetration of the hair color to the cortex of the hair.

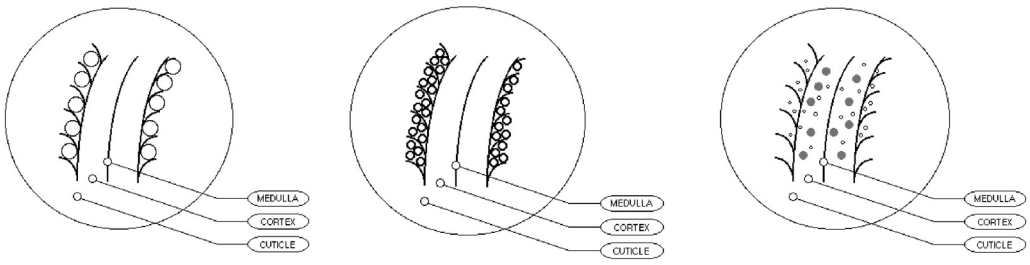
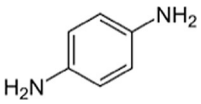
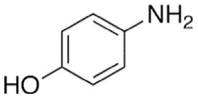
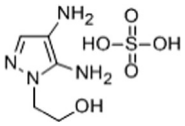
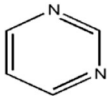
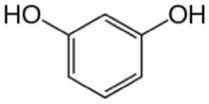
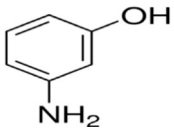
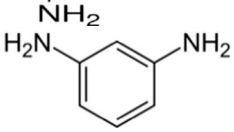
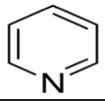



**Fig. 1.** Depth of hair dye penetration based on hair dye type.
Madnani and Khan, 2013.

**Table 1**
A list of the major ingredients in modern hair dye formulations.

| Order | Ingredient | Stature | Health effect | Exposure Limit (mg $m^{-3}$ (Skin)) | Function |
|---|---|---|---|---|---|
| 1 | *Para*-phenylenediamine (PPD) |  | Pharyngeal, laryngeal irritation; bronchial asthma; sensitization dermatitis | [a]PEL: 0.1 [b]TLV: 0.1 [c](TWA) [d]REL: 0.1 (TWA) | Primary intermediate |
| 2 | *Para*-aminophenol |  | Asthma, irritation of the skin and eyes, dermatitis and methemoglobinemia with cyanosis | Not established | |
| 3 | 4,5-Diaminopyrazole |  | Causes serious eye damage, may cause an allergic skin reaction | Not established | |
| 4 | Pyrimidine |  | Eye irritation; dermatitis | Not established | |
| 5 | Resorcinol |  | Irritation of eyes, skin, nose, throat, upper respiratory system; bluish skin, dizziness, drowsiness | TLV:45 (TWA) REL:45 (TWA) | Oxidative coupler |
| 6 | *Meta*-aminophenol |  | Skin sensitization | Not established | |
| 7 | *Meta*-phenylenediamine |  | Irritating to the eyes and skin, may cause effects on the kidneys and blood resulting in renal failure and formation of methemoglobin | TLV: 0.1 (TWA) | |
| 8 | Pyridine |  | Irritation of eyes, skin, respiratory tract; headache, dizziness, insomnia; redness; burning sensation; weakness. | PEL: 15TWA) TLV: 3.2 (TWA) REL: 15(TWA) | |

[a] **PEL**: **Permissible Exposure Limit by the** Occupational Safety and Health Administration (OSHA).
[b] TLV: Threshold Limit Value by the American Conference of Governmental Industrial Hygienists (ACGIH).
[c] TWA: Time weighted average.
[d] REL: Recommended Exposure Limit by the National Institute for Occupational Safety and Health (NIOSH).

### 3.1. p-Phenylenediamine (PPD)

*Para*phenylenediamine (PPD) is one of the most widely used chemical substances for permanent hair dye (Lopez et al., 2014). It can also be found in many other coloring products like textile (or fur) dyes, dark colored cosmetics, temporary tattoos, photographic developer, lithography plates, photocopying, printing inks, black rubber, oils, greases, and gasoline (Madnani and Khan, 2013). The American Contact Dermatitis Society (ACDS) declared PPD as the Contact Allergen of the Year in 2006 (DeLeo, 2006). Mild reactions caused by the use of hair dye usually involve dermatitis to the upper eyelids or the rims of the ears (Gupta et al., 2015). In more severe cases, there may be marked reddening and swelling of the scalp and the face (Gupta et al., 2015). People working with PPD (such as hairdressers and film developers) may develop dermatitis on their hands, and under such circumstances patch testing usually reveals hypersensitivity to PPD (Wilkinson and Beck, 2010).

Some newer permanent and semi-permanent hair dyes use para-toluenediamine sulfate (PTDS) instead of PPD (Madnani and Khan, 2013). This is likely to be tolerated by about 50% of people who are allergic to PPD (Scheman et al., 2011). Most individuals not allergic to PTDS will also test negative to other substances in the dye series (Scheman et al., 2011). The reported prevalence of positive patch test reactions to PPD among dermatitis patients is 4.4% in Asia, 4.1% in Europe, and 6.0% in North America (Thyssen et al., 2008). Rubin et al. (2010) found that hair dyes containing PPD are potent immune activators that can lead to severe contact hypersensitivity in mice. However, they stated that a minority of people exposed to permanent hair dye should develop symptomatic contact hypersensitivity. Likewise, PPD happens to cause delayed-type hypersensitivity, involving a cytokine response and local infiltration of T-cell subpopulations, resulting in contact dermatitis (Svalgaard et al., 2014). Fig. 2 shows a few examples of PPD contact dermatitis.

### 3.2. toluene-2,5-diamine (PTD)

Toluene-2,5-diamine (PTD) is one of the most frequently used oxidative hair dyes (Schmidt et al., 2014). Consumer-available PTD-containing permanent hair dyes can be potent immune activators to induce both pro- and anti-inflammatory responses (Schmidt et al., 2014). However, relatively little is yet known about the immune response to oxidative hair dyes containing PTD. The hair dye containing 1·60% PTD was shown to induce strong local inflammation and caused T- and B-cell infiltration and proliferation as well as an increased number of regulatory T cells in the draining lymph nodes (Schmidt et al., 2014). In contrast, hair dye containing 0·48% PTD induced skin inflammation, while causing only minor responses in the draining lymph nodes (Schmidt et al., 2014). Burnett et al. (2010) found PTD (up to 3%) and PTD sulfate (up to 4%) in 79 and 168 products, respectively. The concentrations of these two compounds in hair dye ingredients

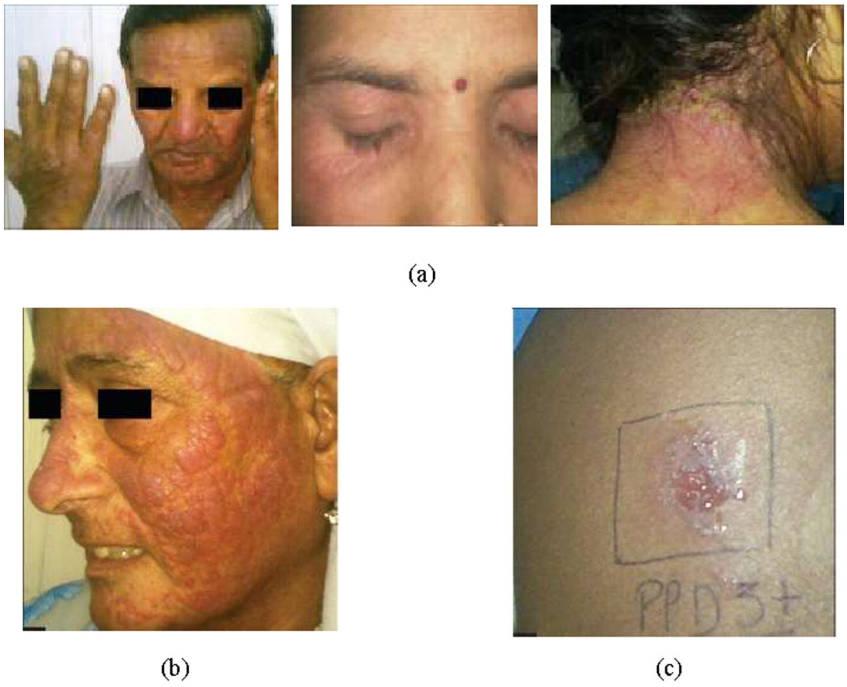



**Fig. 2.** Pictures of skin problems due to PPD exposure: (a) PPD contact dermatitis localized to different parts of the body, (b) chronic actinic dermatitis (actinic reticuloid) due to PPD, and (c) patch test for a 3+ reaction to PPD.
Gupta et al., 2015.

were considered in a range safe for use in present practice (Burnett et al., 2010).

## 4. Adverse health effects

Hair dyeing products are identified as the cause of various adverse health effects, especially allergic contact dermatitis (Handa et al., 2012). In addition, its association with more serious and systemic disease including cancer has also been suggested (Andrew et al., 2004; Mendelsohn et al., 2009). In one study focusing on adverse hair dye reactions, a total of 110 volunteers (out of 263) in India were found to suffer from adverse reactions, mainly headache (63%) and itching (38%) (Fig. 3) (Patel et al., 2013).

### *4.1. Skin irritation and allergy*

As hair-dye products contain a wide range of chemicals, some individuals are found to experience allergic reactions and/or skin irritation more severely than others (Hamann et al., 2014). Symptoms of these reactions can include redness, sores, itching, burning sensation, and discomfort. Local skin irritation is recognized to stimulate the scalp, neck, forehead, ears, and eyelids (Hamann et al., 2014). Such symptoms may not be immediately apparent following application and processing of the tint; they could instead arise after a few hours or even a day later. PPD found in permanent hair dyes is known to act as a strong sensitizer in some people (Scheman et al., 2011). To date, the majority of hair-color product advertisements have recommend the use of patch tests (e.g., mixing a small quantity of tint for the direct skin application for a period of 48 h) for their clients before using the product (Søsted et al., 2013). However, according to Thyssen et al. (2012), such tests should be considered diagnostic tests rather than screening tests. The EU Scientific Committee on Consumer Products pointed out that such tests may be misleading to show false-negative results; it can take up to a week to react to the allergen instead of 48 h (SCCP, 2006).

Hair dyes may be a source of skin sensitizers, causing contact allergy and dermatitis in hairdressers and consumers (Yazar et al., 2012). Hair dyes induce anti-inflammatory mechanisms and are potent skin sensitizers to activate inflammatory T cells (Rubin et al., 2010). This might explain why many consumers can use hair dyes repeatedly without developing noticeable allergies. Yazar et al. (2012) identified a total of 25 different hair dye substances categorized as potent skin sensitizers such that 87% of 105 products contained at least four of the substances. Among hair dye users, a few cases of Type 1 (IgE-mediated) allergic responses associated with PPD or PTD have been reported (Rothe et al., 2011).

As part of an effort to determine whether repeated dermal exposure to hair dyes could induce a T-helper-2 (T(H)2) response, a dermal exposure regimen was used to identify a T(H)2 response in the mouse model. Rothe et al. (2011) observed ear swelling in mice at post-final exposure to PPD and PTD, indicating the signal of an immune response. Although current animal models have a limited ability to detect rare T(H)2 responses to contact allergens, results of one study supported

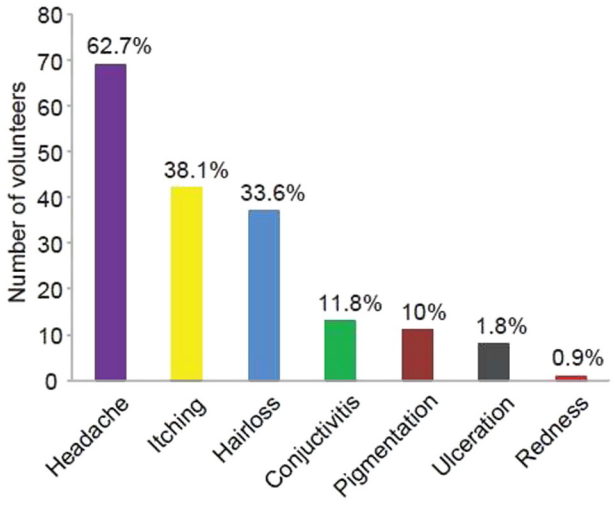



**Fig. 3.** Adverse reactions due to the use of hair dyes in humans.
Patel et al., 2013.

the view that exposure to hair dyes may not be directly associated with relevant T(H)2 induction (Rothe et al., 2011). In a previous study, permanent hair dyes containing PPD were used in a modified version of the local lymph node assay in the mouse model. It was assumed that PPD-containing permanent hair dyes would be potent and rapid immune activators, and mixing of the color gel and developer (oxidant) would increase the induction of skin inflammation relative to safe application of the color gel (Bonefeld et al., 2010). In a study conducted in the USA, at least one potent sensitizer was found in 106 out of 107 hair dye products (Hamann et al., 2014). These authors identified PPD in 78%, resorcinol in 89%, m-aminophenol in 75%, p-aminophenol in 60%, and toluene-2,5-diamine in 21% of the tested products. Søsted et al. (2013) studied 2939 consecutive patients in 12 dermatology clinics who undertook patch tests with five hair dyes available from patch test suppliers. Furthermore, 22 subjects frequently used hair dye ingredients that are not commonly available from patch test suppliers, which were also tested in subgroups of ~500 patients each. They found a positive reaction to PPD in 4.5% of patients, while reactions were observed at 2.8% for PTD, 1.8% for p-aminophenol, 1% for m-aminophenol, and 0.1% for resorcinol with a sum total of 5.3%. Helaskoski et al. (2014) reported a total of 11 hairdressers with occupational asthma (5 cases), rhinitis (5 cases), and contact urticaria (3 cases) due to the handling or use of hair dyes. They also found that 9 hairdressers had positive results out of the 52 (17%) specific inhalation challenges performed.

### 4.2. Cancer

A number of components contained in hair dye products are suspected to cause cancer, although none are yet specifically identified in that respect. The use of hair dyes has been suggested as a risk factor for several types of cancer in epidemiologic studies. Such alarming findings and controversial declarations by scientific organizations (and the general media) showed lines of evidence for relative risk estimates along with confidence intervals (CIs) by the use of personal hair dye (Takkouche et al., 2005). They did not find strong linkage between personal hair dye users and the risk of cancer.

In some studies, an increased risk of bladder cancer was suggested to arise due to the use of permanent hair dyes (Gago-Dominguez et al., 2001; Andrew et al., 2004; Koutros et al., 2011). In contrast, such evidence was not found in a number of other studies (Kogevinas et al., 2006; Kelsh et al., 2008; Koutros et al., 2011; Turati et al., 2014). According to the meta-analysis of 11 case–control studies and one cohort study, no association between personal hair dye use and bladder cancer among women (meta-relative risk [mRR] = 1.01, 95% CI: 0.89–1.14), men (mRR = 0.82, 95% CI: 0.60–1.14), or both sexes combined (mRR = 0.97, 95% CI: 0.87–1.08) was found (Kelsh et al., 2008). However, owing to the small sample size taken for such studies, the results were not convincing enough to yield consistent data sets (Harling et al., 2010). Based on a review of 42 studies, an increased risk for bladder cancer with statistical significance (among hairdressers) was observed from those with more than 10 years of experience (Harling et al., 2010). In a meta-analysis study, Takkouche et al. (2009) reported the pooled relative risk of occupational exposure of a hairdresser as 1.27 (95% CI 1.15-1.41) for lung cancer, 1.52 [95% CI 1.11-2.08] for larynx cancer, 1.30 (95% CI 1.20-1.42) for bladder cancer, and 1.62 (95% CI 1.22-2.14) for multiple myeloma.

A study in New England, USA, reported that women who used permanent dyes were seen to have an increased risk of bladder cancer (Koutros et al., 2011). In a case–control study based on a population of the Netherlands (involving 1385 cases ($n = 246$ women) and 4754 controls ($n = 2587$ women)), the use of either temporary (OR, 0.77; 95% CI, 0.58–1.02) or permanent hair dyes (OR, 0.87; 95% CI, 0.65–1.18) was not associated with the risk of bladder cancer (Ros et al., 2012). In another meta-analysis of case–control ($n = 15$) and cohort ($n = 2$) studies, no association of bladder cancer was observed in the highest category with respect to the duration of use and lifetime frequency of using any type of hair dye (Turati et al., 2014). As such, further investigations are desirable with the expansion of sample sizes. With the aid of such efforts, one may be able to address the role of classified subgroups that may be more prone to the toxic effects of hair dyes. Although the use of hair dye may not provide sufficient evidence for specific cancer risk, it may be possible to identify a small risk associated with certain cancers. More studies focusing on hairdressers who are routinely exposed to the chemicals in hair dyes may shed more light on such connections. However, according to IARC, the most dominant route of exposure to hazardous components of hair dye is through dermal contact (IARC, 2010). As hairdressers nowadays commonly wear gloves when handling hair dyes, the central focal point of study should be placed on the frequent users of hair dye products in general.

## 5. Regulations

Following modern trends, people have begun to dye their hair at increasingly earlier ages, exposing them to strongly sensitizing substances that can potentially increase the risk of allergic reactions via many possible routes. The European Union (EU) Scientific Committee on Consumer Products (SCCP) foresees the banning of all permanent and non-permanent hair dyes for which the industry has not submitted a safety file for added substances that the SCCP has deemed as chemicals of interest since 2003 (SCCP, 2006). A considerably large number of ingredients are not permitted for use in hair-dye products in the EU (SCCP, 2006). Likewise, under the Food, Drug, and Cosmetic Act (FD&C Act) passed by US Congress, the Food and Drug Administration (FDA) must approve the use of color additives (USFDA, 2013). Accordingly, warnings on the use of strong sensitizers (including PPD, PTD, and resorcinol) in hair dyes must be provided in product packaging (US FDA, 2013), and the labeling must be supplemented to draw consumers' attention to the warning. Since 2011, the European Environment Agency (EEA) has prohibited the manufacturing and import of hair dyes that do not feature new labeling to address that such products should not be used by persons under the age of 16 (EEA, 2011).

According to the regulation laws, it is the manufacturer's responsibility to substantiate that the product and all of its ingredients are safe for consumers under the intended conditions of use. All pieces of information supporting the safety of a product should be kept by the manufacturers and available to the authorities upon request. As such, manufacturers have, for many years, been submitting the safety data on hair colorants to independent scientific bodies such as the European Commission's Scientific Committee on Consumer Products (SCCP) and the US Cosmetic Ingredient Review Expert Panel (CIR) so that they can deliver independent scientific opinions (Orton and Basketter, 2012). In Japan, the regulation of cosmetic products is enforced in the most restrictive way. As all cosmetic products are considered equivalent to drugs, hair dye products are subject to premarket approval by the Ministry of Health and Welfare. These products are only allowed to contain ingredients included in the Comprehensive Licensing Standards (CLS) of Cosmetics by Category and these ingredients must conform to certain types of defined specifications (MHLW, 2007). In other Asian countries (e.g. Republic of Korea and China), regulatory requirements similar to those in Japan have also been developed and introduced for hair dyes to confine the use of certain ingredients (Nohynek et al., 2010).

## 6. Conclusion

Some components in hair dyes have been categorized as sensitizers because repetitive exposure to such substances is suspected to cause an allergic reaction or more serious disease. This is the reason why consumers of hair dye products are recommended to perform allergy testing 48 h before applying the formulation to their hair to guard against severe allergic reactions. Cancer risk from some of the chemicals in hair dyes has also been debated, although no definitive conclusion has

been drawn relative to the carcinogenic nature of hair dye products. However, a number of studies have indicated the strong possibility that people working in the hairdressing industry are likely to suffer from bladder cancer more significantly based on the findings of statistical correlations. For those who dye their own hair at home, evidence of the connection between cancer incidences due to the use of dyes is insufficient or inconsistent. As such, extended efforts are required to clearly address the significance of hair dying carried out in the public domain. In reality, many cases of dermatitis caused by the use of hair dye could have been overlooked, and severe dermatitis could have lasted for a longer period of time. Thus, it is important that hair dye users have proper knowledge about the product contents, instructions regarding the use of the given product on the package itself, and the various potential side effects.

## Acknowledgment

We acknowledge the support from a National Research Foundation of Korea (NRF) grant funded by the Ministry of Education, Science and Technology (MEST) (No. 2009-0093848).

## References

Andrew, A.S., Schned, A.R., Heaney, J.A., Karagas, M.R., 2004. Bladder cancer risk and personal hair dye use. Int. J. Cancer 109 (4), 581–586.
Bolt, H.M., Golka, K., 2007. The debate on carcinogenicity of permanent hair dyes: new insights. Crit. Rev. Toxicol. 37 (6), 521–536.
Bonefeld, C.M., Larsen, J.M., Dabelsteen, S., Geisler, C., White, I.R., Menné, T., Johansen, J.D., 2010. Consumer available permanent hair dye products cause major allergic immune activation in an animal model. Br. J. Dermatol. 162 (1), 102–107. http://dx.doi.org/10.1111/j.1365-2133.2009.09417.x (2010 Jan, Epub 2009 Jul 20).
Burnett, C.L., Bergfeld, W.F., Belsito, D.V., Klaassen, C.D., Marks Jr., J.G., Shank, R.C., Slaga, T.J., Snyder, P.W., Alan, Andersen F., 2010. Final amended report of the safety assessment of toluene-2,5-diamine, toluene-2,5-diamine sulfate, and toluene-3,4-diamine as used in cosmetics. Int. J. Toxicol. 29 (3 Suppl.), 61S–83S. http://dx.doi.org/10.1177/1091581810361964 (2010 May).
DeL eo, V.A., 2006. Contact allergen of the year: p-phenylenediamine. Dermatitis 17 (2), 53–55.
European Environment Agency (EEA), 2011. Consolidated EU Cosmetics Directive and subsequent adaptations. available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1976L0768:20100301:en:PDF (Accessed August 21, 2015).
Gago-Dominguez, M., Castelao, J.E., Yuan, J.M., Yu, M.C., Ross, R.K., 2001. Use of permanent hair dyes and bladder-cancer risk. Int. J. Cancer 91 (4), 575–579.
Gupta, M., Mahajan, V.K., Mehta, K.S., Chauhan, P.S., 2015. Hair dye dermatitis and *p*-phenylenediamine contact sensitivity: a preliminary report. Indian Dermatol. Online J. 6 (4), 241–246. http://dx.doi.org/10.4103/2229-5178.160253 (2015 Jul-Aug).
Hamann, D., Yazar, K., Hamann, C.R., Thyssen, J.P., Lidén, C., 2014. p-Phenylenediamine and other allergens in hair dye products in the United States: a consumer exposure study. Contact Dermatitis 70 (4), 213–218. http://dx.doi.org/10.1111/cod.12164 (2014 Apr).
Handa, S., Mahajan, R., De, D., 2012. Contact dermatitis to hair dye: an update. Indian J. Dermatol. Venereol. Leprol. 78, 583–590.
Harling, M., Schablon, A., Schedlbauer, G., Dulon, M., Nienhaus, A., 2010. Bladder cancer among hairdressers: a meta-analysis. Occup. Environ. Med. 67 (5), 351–358.
Helaskoski, E., Suojalehto, H., Virtanen, H., Airaksinen, L., Kuuliala, O., Aalto-Korte, K., Pesonen, M., 2014. Occupational asthma, rhinitis, and contact urticaria caused by oxidative hair dyes in hairdressers. Ann. Allergy Asthma Immunol. 112 (1), 46–52. http://dx.doi.org/10.1016/j.anai.2013.10.002 (2014 Jan, Epub 2013 Oct 30).
International Agency for Research on Cancer, 2010. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 99: Some Aromatic Amines, Organic Dyes, and Related Exposures 2010 (Accessed at http://monographs.iarc.fr/ENG/Monographs/vol99/index.php).
Kelsh, M.A., Alexander, D.D., Kalmes, R.M., Buffler, P.A., 2008. Personal use of hair dyes and risk of bladder cancer: a meta-analysis of epidemiologic data. Cancer Causes Control 19 (6), 549–558.
Kim, J.E., Jung, H.D., Kang, H., 2012. A survey of the awareness, knowledge and behavior of hair dye use in a Korean population with gray hair. Ann. Dermatol. 24, 274–279.
Kogevinas, M., Fernandez, F., Garcia-Closas, M., 2006. Hair dye use is not associated with risk for bladder cancer: evidence from a case–control study in Spain. Eur. J. Cancer 42 (10), 1448–1454.
Koutros, S., Silverman, D.T., Baris, D., 2011. Hair dye use and risk of bladder cancer in the New England bladder cancer study. Int. J. Cancer 2011. http://dx.doi.org/10.1002/ijc.26245.
Lewis, D., Mama, J., Hawkes, J., 2013. A review of aspects of oxidative hair dye chemistry with special reference to n-nitrosamine formation. Material 6, 517–534.
Lopez, I.E., Turrentine, J.E., Cruz Jr., P.D., 2014. Clues to diagnosis of connubial contact dermatitis to paraphenylenediamine. Dermatitis 25 (1), 32–33.
Madnani, N., Khan, K., 2013. Hair cosmetics. Symp.-Hair Disord. 79 (5), 654–667.
Mendelsohn, J.B., Li, Q.Z., Ji, B.T., Shu, X.O., Yang, G., Li, H.L., 2009. Personal use of hair dye and cancer risk in a prospective cohort of Chinese women. Cancer Sci. 100, 1088–1091.
MHLW, 2007. Ministry of Health Labor and Welfare, Tokyo, Japan. Quasi drugs. Available at: http://www.mhlw.go.jp/english/links/index.html.
National Cancer Institute (NCI), 2014. Hair dyes and cancer risk. 2011. Accessed at http://www.cancer.gov/cancertopics/factsheet/Risk/hair-dyes.
Nohynek, G.J., Antignac, E., Re, T., Toutain, H., 2010. Safety assessment of personal care products/cosmetics and their ingredients. Toxicol. Appl. Pharmacol. 243 (2010), 239–259.
Orton, D., Basketter, D., 2012. Hair dye sensitivity testing: a critical commentary. Contact Dermatitis 66 (6), 312–316. http://dx.doi.org/10.1111/j.1600-0536.2012.02095.x.
Patel, D., Narayana, S., Krishnaswamy, B., 2013. Trends in use of hair Dye: a cross-sectional study. Int. J. Trichol. 5, 140–143.
Ros, M.M., Gago-Dominguez, M., Aben, K.K.H., Bueno-de-Mesquita, H.B., Kampman, E., Vermeulen, S.H., Kiemeney, L.A., 2012. Personal hair dye use and the risk of bladder cancer: a case–control study from The Netherlands. Cancer Causes Control 23 (7), 1139–1148.
Rothe, H., Sarlo, K., Scheffler, H., Goebel, C., 2011. The hair dyes PPD and PTD fail to induce a T(H)2 immune response following repeated topical application in BALB/c mice. J. Immunotoxicol. 8 (1), 46–55. http://dx.doi.org/10.3109/1547691X.2010.543096.
Rubin, I.M., Dabelsteen, S., Nielsen, M.M., White, I.R., Johansen, J.D., Geisler, C., Bonefeld, C.M., 2010. Repeated exposure to hair dye induces regulatory T cells in mice. Br. J. Dermatol. 163 (5), 992–998.
SCCP (Scientific Committee on Consumer Products), 2006. Review of the SCCNFP opinion on Hair Dye Strategy in the light of additional information. Adopted by the SCCP During the 8th Plenary Meeting of 20 June 2006 (http://europa.eu.int/comm/enterprise/cosmetics/doc/hairdyestrategyinternet.pdf).
Scheman, A., Cha, C., Bhinder, M., 2011. Alternative hair-dye products for persons allergic to para-phenylenediamine. Dermatitis 22 (4), 189–192.
Schmidt, J.D., Johansen, J.D., Nielsen, M.M., Zimersson, E., Svedman, C., Bruze, M., Engkilde, K., Poulsen, S.S., Geisler, C., Bonefeld, C.M., 2014. Immune responses to hair dyes containing toluene-2,5-diamine. Br. J. Dermatol. 170 (2), 352–359. http://dx.doi.org/10.1111/bjd.12676 (2014 Feb).
Søsted, H., Rustemeyer, T., Gonçalo, M., Bruze, M., Goossens, A., Giménez-Arnau, A.M., Le Coz, C.J., White, I.R., Diepgen, T.L., Andersen, K.E., Agner, T., Maibach, H., Menné, T., Johansen, J.D., 2013. Contact allergy to common ingredients in hair dyes. Contact Dermatitis 69 (1), 32–39. http://dx.doi.org/10.1111/cod.12077 (2013 Jul).
Svalgaard, J.D., Særmark, C., Dall, M., Buschard, K., Johansen, J.D., Engkilde, K., 2014. Systemic immunogenicity of para-phenylenediamine and diphenylcyclopropenone: two potent contact allergy-inducing haptens. Immunol. Res. 58 (1), 40–50. http://dx.doi.org/10.1007/s12026-013-8482-z (2014 Jan).
Takkouche, B., Etminan, M., Montes-Martinez, A., 2005. Personal use of hair dyes and risk of cancer: a meta-analysis. JAMA 293 (20), 2516–2525.
Takkouche, B., Regueira-Méndez, C., Montes-Martínez, A., 2009. Risk of cancer among hairdressers and related workers: a meta-analysis. Int. J. Epidemiol. 38 (6), 1512–1531. http://dx.doi.org/10.1093/ije/dyp283.
The Economist, 2015. Hair dye—fast-growing business. Accessed at http://www.economist.com/node/631692.
Thyssen, J.P., White, J.M., JP, Thyssen, JM, White, 2008. European Society of Contact Dermatitis. Epidemiological data on consumer allergy to *p*-phenylenediamine. Contact Dermatitis 59, 327–343.
Thyssen, J.P., Søsted, H., Uter, W., Schnuch, A., Giménez-Arnau, A.M., Vigan, M., Rustemeyer, T., Granum, B., McFadden, J., White, J.M., White, I.R., Goossens, A., Menné, T., Lidén, C., Johansen, J.D., 2012. Self-testing for contact sensitization to hair dyes—scientific considerations and clinical concerns of an industry-led screening programme. Contact Dermatitis 66 (6), 300–311. http://dx.doi.org/10.1111/j.1600-0536.2012.02078.x (2012 Jun).
Turati, F., Pelucchi, C., Galeone, C., Decarli, A., La-Vecchia, C., 2014. Personal hair dye use and bladder cancer: a meta-analysis. Ann. Epidemiol. 24 (2), 151–159.
US Food and Drug Administration, 2013. Hair dye and hair relaxers. Accessed at www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118527.htm (Accessed August 29, 2015).
US Food and Drug Administration, 2014. Cosmetics safety Q&A: hair dyes. Accessed at www.fda.gov/cosmetics/resourcesforyou/consumers/ucm167436.htm.
Wilkinson, S.M., Beck, M.H., 2010. Contact Dermatitis-allergic: *p*-phenylenediamine and related dyes. In: Tony, B., Stephen, B., Neil, C., Christopher, G. (Eds.), Rook's Textbook of Dermatology, eighth ed. 2010. Blackwell Publishing, Oxford, pp. 26.60–26.62.
Yazar, K., Boman, A., Lidén, C., 2012. p-Phenylenediamine and other hair dye sensitizers in Spain. Contact Dermatitis 66 (1), 27–32. http://dx.doi.org/10.1111/j.1600-0536.2011.01979.x (Epub 2011 Nov 15).