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Review

Hair Dye Ingredients and Potential Health Risks from Exposure to Hair Dyeing

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Lin He, Freideriki Michailidou, Hailey L. Gahlon, and Weibin Zeng*

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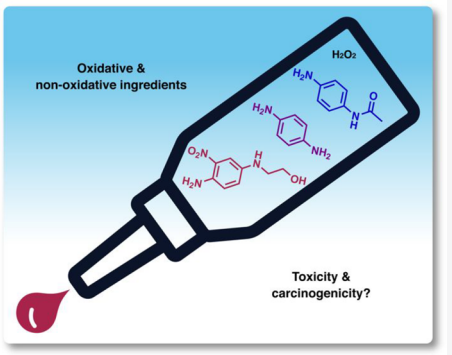
ABSTRACT: Given the worldwide popularity of hair dyeing, there is an urgent need to understand the toxicities and risks associated with exposure to chemicals found in hair dye formulations. Hair dyes are categorized as oxidative and nonoxidative in terms of their chemical composition and ingredients. For several decades, the expert panel's Cosmetic Ingredient Review (CIR) has assessed the safety of many of the chemicals used in hair dyes; however, a comprehensive review of hair dye ingredients and the risk of exposure to hair dyeing has not been documented. Herein, we review the safety of the various chemicals in oxidative and nonoxidative hair dyes, toxicities associated with hair dyeing, and the carcinogenic risks related to hair dyeing. While many compounds are considered safe for users at the concentrations in hair dyes, there are conflicting data about a large number of hair dye formulations. The CIR expert panel has ratified a number of coloring ingredients for hair dyes and banned a series of chemicals as carcinogenic to animals and unsafe for this application. The use of these chemicals as raw materials for producing hair dyes may result in the synthesis of other contaminants with potential toxicities and increased risk of carcinogenesis. It is an open question whether personal or occupational hair dyeing increases the risk of cancer; however, in specific subpopulations, a positive association between hair dye use and cancer occurrence has been reported. To address this question, a better understanding of the chemical and mechanistic basis of the reported toxicities of hair dye mixtures and individual hair dye ingredients is needed. It is anticipated that in-depth chemical and systems toxicology studies harnessing modern and emerging techniques can shed light on this public health concern in the future.



1. INTRODUCTION

About 33% of women over the age of 18 and more than 10% of men over age 40 in Europe and the United States dye their hair.[1] Given this popularity, it is critical to assess the toxicity and carcinogenicity of hair dyes and their ingredients. Thanks to the expert panel's Cosmetic Ingredient Review (CIR), a large number of candidate coloring ingredients have undergone safety assessment prior to use in hair dyes.

Modern hair dyes are classified as oxidative or nonoxidative, and their color durability is referred to as temporary (8−12 washings), semipermanent (∼24 washings), or permanent (until hair grows out), in terms of their formulation (Table 1).[2] As far as the chemical composition is concerned, oxidative hair dye products are often referred to as permanent or semi-permanent, while nonoxidative hair dye products are considered temporary or semipermanent. Nonoxidative compounds are used in temporary and semipermanent hair dyes, which are used to directly dye natural hair.[2−4] Oxidative dyes were introduced as permanent hair dyes at the end of the 19th century and experienced explosive growth after 1970; a variety of new permanent oxidative chemical hair dyes currently dominate the global hair dye market. Permanent hair dyes account for the highest market share of all modern hair dyes in Asia, America, and Europe.[5]

Because of the increasing number of users and the growing economic share, hair dyeing has been pinpointed as a public health concern, urgently needing evaluation of the toxicity and carcinogenicity related to hair dyes. Because different hair dye types with specific compounds have been employed, results of hair dye-induced toxicity and carcinogenicity reported in the literature have been inconclusive. This article reviewed the existing literature and available data on the safety and risks associated with established chemicals in hair dyes. We related these compounds to their reported toxicities and carcinogenic risks, identified the current gaps of knowledge in the field, and proposed future directions.

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Table 1. Category and Composition of Modern Hair Dyes

dye category	hair coloring process	composition	hair dyeing type
temporary	nonoxidative	water-soluble acidic and basic dyes bearing azo or anthraquinone groups	deposition on hair
semipermanent	nonoxidative	acid and basic dyes bearing azo groups, anthraquinones, triphenylmethanes and nitro derivatives as chromophores	ionic interactions or van der Waals forces
permanent	oxidative	precursor agent, coupling agent and oxidizer	penetration into hair

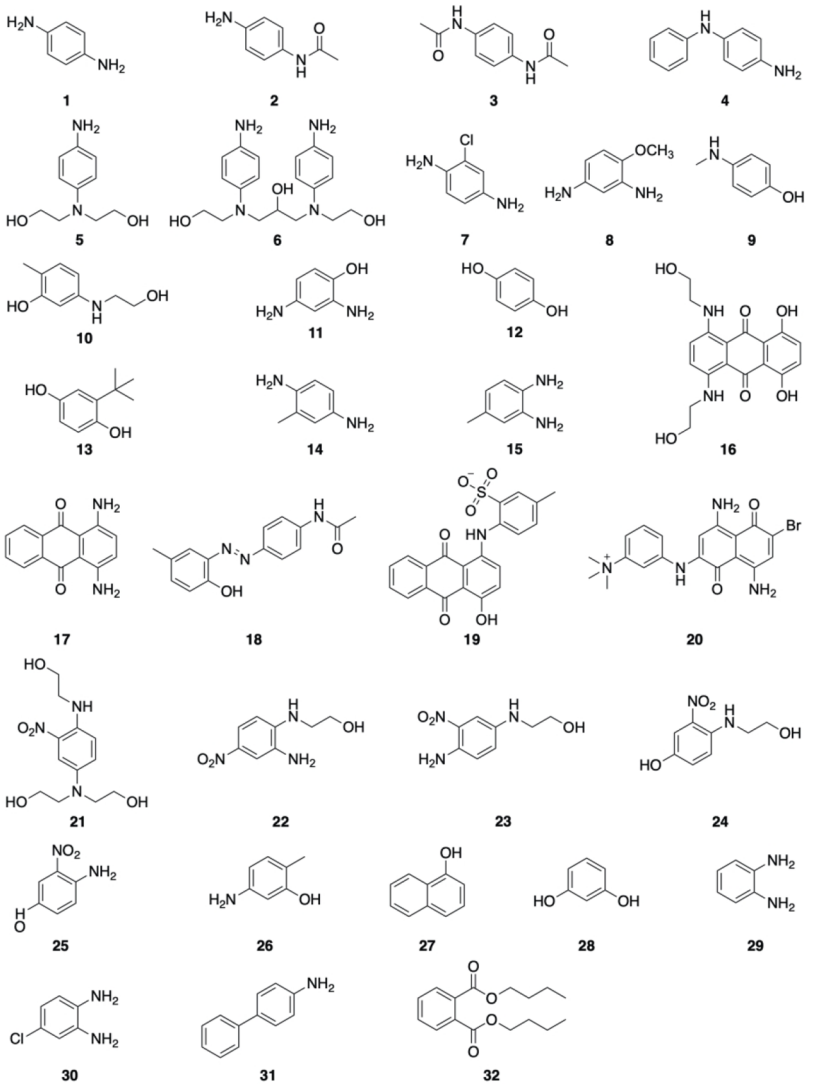

Figure 1. Chemical structures of hair dye ingredients. Chemical structures of the following hair dye ingredients are shown: *p*-phenylenediamine **1** (PPD), *N*-monoacetyl-*p*-phenylenediamine **2** (MAPPD), *N*,*N*-diacetyl-p-phenylenediamine **3** (DAPPD), *N*-phenyl-*p*-phenylenediamine **4**, *N*,*N*-bis(hydroxyethyl)-*p*-phenylenediamine **5**, hydroxypropyl bis(*N*-hydroxyethyl-p-phenylenediamine) **6**, 2-chloro-*p*-phenylenediamine **7**, 4-methoxy-*m*-phenylenediamine **8**, *p*-methylaminophenol **9**, 2-methyl-5-hydroxyethylaminophenol **10**, 2,4-diaminophenol **11**, hydroquinone **12**, *t*-butyl hydroquinone **13**, toluene-2,5-diamine (CAS no: 95-70-5) **14**, toluene-3,4-diamine **15**, Disperse Blue 7 **16**, Disperse Violet 1 **17**, Disperse Yellow 3 **18**, Acid Violet 43 **19**, Basic Blue 99 **20**, HC Blue no. 2 **21**, HC Yellow no. 5 **22**, HC Red no. 7 **23**, 3-nitro-*p*-hydroxyethylaminophenol **24**, 4-amino-3-nitrophenol **25**, 4-amino-2-hydroxytoluene **26**, 1-naphthol **27**, resorcinol **28**, *o*-phenylenediamine **29**, 4-chloro-*o*-phenylenediamine **30**, 4-aminobiphenyl **31**, and di-*n*-butyl phthalate **32**. Only the core chemical structures are shown. The sulfate or hydrochloride salts are omitted for simplicity.

2. HAIR DYE INGREDIENTS

2.1. Hair Dye Categories. The chemical ingredients of hair dyes vary among formulations that involve oxidative reactions to achieve coloring and those using nonoxidative processes.[2] Temporary and semipermanent hair dyes typically rely on nonoxidative processes, while permanent hair dyes rely on oxidative reactions (Table 1). Temporary hair dyes are composed of water-soluble acidic and basic dyes bearing azo or anthraquinone groups; they are generally regarded as more benign because they are deposited on the hair surface and do not penetrate into the hair cortex. They do not require an oxidizing agent and are typically removed by a single shampooing.[3,4] Semipermanent hair dyes consist of acidic and basic dyes bearing azo groups, anthraquinones, triphenyl methanes, or nitro derivatives as chromophores. Ionic

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Table 2. Detailed Characteristics of Major Hair Dye Ingredients[a]

compound	year[b]	maximum allowable concentration (%)	LD_{50} (mg/kg)[c]	toxicity	carcinogenicity	ref
N,*N*-bis(hydroxyethyl)-*p*-phenylenediamine **5** sulfate salt	1984	≤5	264	reduced body weight; darkened thyroid glands; decreased serum iron concentration; delayed hypersensitivity; allergic contact dermatitis	no evidence	10
N-phenyl-*p*-phenylenediamine **4**, *N*-phenyl-*p*-phenylenediamine HCl	1993	≤1.7	464−1000	reduced body weight; degenerated seminiferous tubules; skeletal malformations; skin irritation	no evidence	11
hydroxypropyl bis(*N*-hydroxyethyl-*p*-phenylenediamine) **6** HCl	NA	≤0.4	2186	reduced body weight, mean serum glucose and total protein levels; reproductive and developmental toxicity	no evidence	12
4-methoxy-*m*-phenylenediamine **8**, 4-methoxy-*m*-phenylenediamine sulfate salt, 4-methoxy-*m*-phenylenediamine HCl	1978	NA	400−500	skin irritation; mutagenicity	animal carcinogenicity	13
2-chloro-*p*-phenylenediamine **7**, 2-chloro-*p*-phenylenediamine sulfate salt	1984	≤1.0	NA	skin irritation; reduced body weight; ocular irritation	no evidence	14
2-methyl-5-hydroxyethylaminophenol **10**	NA	≤5	5700	skin irritation; mutagenicity; allergic contact dermatitis	no evidence	15
p-methylaminophenol **9** sulfate salt	NA	≤1	NA	increased rate of formation of methemoglobin; skin irritation	no evidence	16
2,4-diaminophenol **11**, 2,4-diaminophenol dihydrochloride salt	1993	≤0.2	240	skin irritation; severe ocular irritation; mutagenicity	no evidence	17
hydroquinone **12**	1981	≤1	627−743	nephrotoxicity; cytotoxicity; skin irritation; skin sensitization; skin depigmentation; mutagenicity	animal carcinogenicity	18, 19
t-butyl hydroquinone **13**	1981	≤0.1	480−800	reduced body weights; mutagenicity	no evidence	20
toluene-2,5-diamine **14**, toluene-2,5-diamine sulfate salt	1984	≤4	98−102	skin irritation; skin sensitization; ocular irritation; reproductive toxicity; skeletal malformation	no evidence	21−23
toluene-3,4-diamine **15**	1984	NA	NA	duodenal lesions; genotoxicity; skin sensitization	no evidence	21, 22
Disperse Blue 7 **16**	2002	NA	NA	mutagenicity	no evidence	24
Disperse Violet 1 **17**	1988	≤1	NA	ocular irritation	no evidence	25
Disperse Yellow 3 **18**	1992	NA	NA	nephrotoxicity; chromosomal aberrations; allergic contact dermatitis	animal carcinogenicity	26
Acid Violet 43 **19**	1984	≤1	NA	no significant toxicity	no evidence	27
Basic Blue 99 **20**	1992	≤2	>2000	skin irritation	no evidence	28
HC Blue no. 2 **21**	1993	≤1.7	1250−5000	mutagenicity	no evidence	29
HC Yellow no. 5 **22**	2002	≤1.6	555.56	skin irritation	no evidence	30
HC Red no. 7 **23**	2005	≤1	NA	skin sensitization; mutagenicity	no evidence	31

[a]For chemical structures, refer to Figure 1. [b]The first yearly report by the Food and Drug Administration. [c]The oral LD_{50} in rats of aqueous solutions. Abbreviations: LD_{50}, median lethal dose; NA, not assessed.

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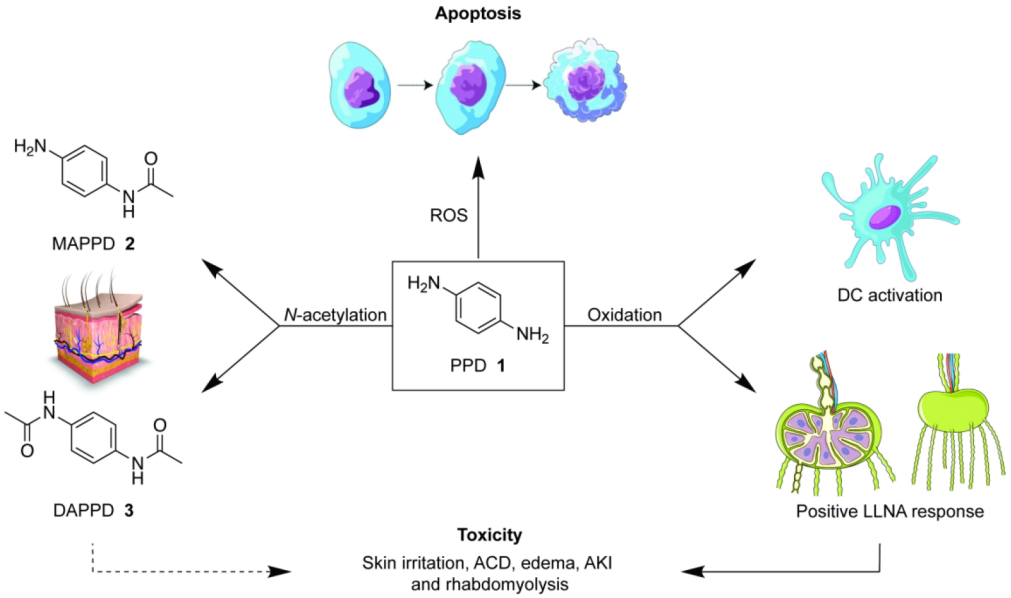

Figure 2. Mechanism of toxicity induced by *p*-phenylenediamine. An increase in reactive oxygen species is associated with PPD **1**-induced apoptosis. Dermal N-acetylation biotransforms PPD toward MAPPD **2** and DAPPD **3**; at concentrations up to 250 μM, it is beneficial to the MAPPD formation, and at the concentration of 250−1000 μM, it is beneficial to the DAPPD formation. MAPPD and DAPPD fail to activate DCs or cause a positive LLNA response, which are considered the markers of extracorporeal and intracorporeal sensitizing potential of chemical compounds. PPD can induce DC activation after exposure to oxygen in air in vitro, and creates an LLNA response in vivo. The sensitizing PPD oxidation provides some effective immune stimulation that is associated with PPD-induced toxicity. Abbreviations: ROS, reactive oxygen species.

interactions or van der Waals forces are associated with the deposition of these low molecular weight compounds on hair structures. The hair color from semipermanent dyes is generally retained over several shampoo applications. Permanent hair dyes penetrate hair to change the natural hair color, and they are more frequently associated with adverse reactions and pose a higher risk to human health. Permanent hair dyes require three components: (1) precursor agents, that is, primary intermediates comprised of *ortho-* (*o-*) and *para-* (*p-*) aromatic amines substituted with amino groups and/or hydroxides; (2) coupling agents that are formed by aromatic compounds *meta-* (*m-*) substituted with electron-donating groups, such as *m*-phenylenediamines, resorcinol, naphthol, and other derivatives; and (3) oxidizing agents in alkaline media, predominantly hydrogen peroxide (H_2O_2) in the presence of ammonia.

2.2. Hair Dye Ingredients: Chemical Characteristics and Reported Toxicities. This section focuses on the physical and chemical characteristics of widely used hair dye chemicals (Figure 1) and the chemical basis of their reported toxicities. Current knowledge regarding their safety (including their relevant hydrochloride and sulfate salts) is summarized in Table 2.[6−27]

Aromatic amines, such as *p*-phenylenediamine (PPD, **1**) (Figures 1 and 2), constitute the main class of compounds used as precursors in permanent hair dyes. The multiple toxicological properties of PPD have been demonstrated in previous studies; for instance, PPD induces apoptosis by increasing reactive oxygen species.[28] During hair coloring, PPD can penetrate the skin and be absorbed by the airway,[29] where it can then be biotransformed into *N*-monoacetyl-*p*-phenylenediamine (MAPPD, **2**) and *N,N′*-diacetyl-*p*-phenylenediamine (DAPPD, **3**) (Figure 2). A study of the transformation of PPD to MAPPD and DAPPD using reconstituted human epidermis showed that the metabolite levels produced depend on the dose of PPD. At concentrations of 250−1000 μM, the formation of MAPPD was favored, while at doses below 250 μM, DAPPD was preferentially formed.[30] PPD induces dendritic cell (DC) activation after in vitro exposure to oxygen in air, and a positive local lymph node assay (LLNA) response in vivo, demonstrating its intracorporeal sensitizing potential. The sensitizers produced by PPD oxidation in both cases induced immune stimulation. In contrast, MAPPD and DAPPD did not induce DC activation or give a positive LLNA response.[31] The biotransformation of PDD to MAPPD or DAPPD and the formation of sensitizers from PPD oxidation are two distinct competing pathways. The formation of sensitizing agents is promoted when increased PPD concentrations are present, leading to a series of PPD-related toxicities (Figure 2).

N-Phenyl-*p*-phenylenediamine **4** (Figure 1, Table 2) is another common aromatic amine present in hair dyes. It has been associated with toxic effects including body weight reduction as a function of dose in rats, degeneration of the seminiferous tubules, skeletal malformation, and skin sensitization (Table 2).[32] The EU Scientific Committee on Consumer Products (SCCP) identified limitations in some of these studies, such as inadequate data inclusion and noncompliance with the Organization for Economic Cooperation and Development guidelines, but confirmed the strong potential of *N*-phenyl-*p*-phenylenediamine to cause skin sensitization.[33] Exposure to the structurally related *N,N*-bis(hydroxyethyl)-*p*-phenylenediamine **5** (sulfate salt) is associated with reduction in body weight, darkening of thyroid glands, decrease in serum iron concentration, delayed hypersensitivity of guinea pig skin, and allergic contact dermatitis (ACD).[6,34] Exposure to hydroxypropyl bis(*N*-hydroxyethyl-*p*-phenylenediamine) hydrochloride salt **6** is linked to reduced body weight, decreased mean serum glucose, attenuated total protein levels, and reproductive and developmental problems,[8] while exposure to

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Table 3. Hair Dye-Related Toxicity from a Case Report Study

toxicity	study duration	sex	age	ingredients	exposure route	symptom timing[a]	patch test concen-tration (%)	positive reaction[c]	ref
ACD	2015	F	50	henna	hair dyeing	4 d	0.01	1+	40
ACD	2005	F	50	3-nitro-*p*-hydroxy ethylaminophenol **24** and 4-amino-3-nitrophenol **25**	hair dyeing	1 d	1.00	1+	43
contact anaphylaxis	2017	F	56	Basic Blue 99 **20**	hair dyeing	10 min	0.10	3+	37
ACD	2009	F	47	4-amino-2-hydroxytoluene **26**	hair dyeing	NA	1.00	2+	44
ACD	2018	F	43	1-naphthol **27**	hair dyeing	2 d	1.00	3+	49
DLE	2016	F	32	*p*-phenylenediamine **1** and toluene-2,5-diamine **14**	hair dyeing	NA	NA	2+	55
angioedema	2018	F	29	*p*-phenylenediamine **1**	hair dyeing	1 d	1.00	3+	61
neck and facial swelling	2016	F	15	*p*-phenylenediamine **1**	hair dyeing	3 d	NA	3+	62
severe facial swelling	2014	F	33	*p*-phenylenediamine **1**	hair dyeing	2 d	NA	4+	63
hair loss	2011	F	41	*p*-phenylenediamine **1**	hair dyeing	1 d	1.00	2+	64
pneumothorax	2011	2F	19 ± 1[b]	*p*-phenylenediamine **1**	consumption	NA	NA	NA	71
rhabdomyolysis	2013	M	3	*p*-phenylenediamine **1**	consumption	2 h	NA	NA	72
rhabdomyolysis	2002−2006	8M + 2F	23.2 ± 7.6[b]	*p*-phenylenediamine **1**	consumption	NA	0.95	NA	73

[a]Symptom timing indicates the duration from exposure to symptoms. [b]These studies describe more than one case, and the age is the mean value. [c]The positive reaction is calculated in terms of the patch test of corresponding ingredients at the patch test concentration. Abbreviations: F, female; M, male; NA, not assessed.

2-chloro-*p*-phenylenediamine **7** and its sulfate salt were linked to skin irritation, reduced body weight and ocular irritation.[10] It should be noted that 4-methoxy-*m*-phenylenediamine **8** and its hydrochloride and sulfate salts are unsafe for use in cosmetic products due to their reported carcinogenicity in rats and mice (Table 2).[9]

Aminophenols are another class of ingredients that are widely used in hair dyes. They are chemically synthesized by the reduction of nitrophenols and can be used as primary intermediates in manufacturing sulfur and azo dyes.[11] They typically undergo reactions with oxidants to produce corresponding imines that can chemically react with coupling agents to produce indophenol dyes.[12] As a primary intermediate, *p*-methylaminophenol **9** (sulfate salt) reacts with hemoglobin at a more rapid rate than *p*-aminophenol to form methemoglobin, a form of oxidized hemoglobin, and slightly irritates rabbit skin but is not considered a dermal sensitizer.[12] The coupling agent, 2-methyl-5-hydroxyethylaminophenol **10** is used in oxidative hair dyes at a concentration of ≤5%. It can be mutagenic, and exposure can cause skin irritation, and allergic contact dermatitis.[11] The Food and Drug Administration (FDA) concluded that the maximum allowable concentration of 2,4-diaminophenol **11** and its dihydrochloride salt for use in hair dyes is 0.2%. Exposure to this compound can lead to slight skin irritation, severe ocular irritation, and mutagenicity (Table 2).[13] Hydroquinone **12** is used as an antioxidant, fragrance, reducing agent, and polymerization inhibitor in hair dyes, skincare products, and lipsticks.[14] Human skin absorbs hydroquinone from both aqueous and alcoholic preparations, and excretion of this compound involves the formation of glucuronide or sulfate conjugates.[15] This chemical may cause nephrotoxicity, cytotoxicity, skin irritation, skin sensitization, skin depigmentation, and mutagenicity.[14] The most noteworthy data are related to its reported animal carcinogenicity, in which an increased incidence of renal tubule cell tumors and leukemia was observed in F344 rats; but so far, such adverse effects on humans have not been described.[15] The acid-catalyzed reaction of hydroquinone with isobutylene or *t*-butanol produces a new crystalline solid, *t*-butyl hydroquinone **13**, an ingredient which can cause mild to moderate toxicity such as reduced body weight and mutagenicity in rats when administered orally or intraperitoneally (Table 2).[16]

Diaminotoluene is chemically prepared from dinitrotoluene via a catalytic hydrogenation procedure or from the reaction of iron, hydrochloric acid, and dinitrotoluene. The two isomers, toluene-2,5-diamine **14** and toluene-3,4-diamine **15**, are primary intermediates that can impart different colors to permanent hair dyes.[17] For example, toluene-2,5-diamine and its sulfate salt can color hair black, brown, gold, or gray, and toluene-3,4-diamine makes hair brown, red, or gold.[17] Toluene-2,5-diamine **14** can be readily absorbed through the skin, but 90% will be excreted within 24 h after absorption, with a half-time excretion of 8 h.[19] These two compounds manifested some adverse effects such as extreme skin sensitization[35] and reproductive toxicity (Table 2); however, a maximum concentration of 2% (calculated as free base) or 3.6% (calculated as sulfate salt) applied to the head was considered safe with regard to systemic toxicity.[35] An Ames test demonstrated that the presence of toluene-2,5-diamine in an oxidative hair dye may cause mutagenicity in the TA98 test strain.[36] Further studies are needed to determine the safety of toluene-3,4-diamine as a hair dye ingredient.

Many nonoxidative ingredients are used in temporary and semipermanent hair dyes.[20−27] The CIR concluded that there is insufficient data available regarding the safety of Disperse Blue 7.[20] Disperse Blue 7 **16** is an anthraquinone-based dye used as a hair ingredient in a few selected hair dyes. Disperse Violet 1 **17** is a diamino-anthraquinone dye used in temporary and semipermanent hair dyes at a maximum concentration of 1%. To date, the only toxicity reported is ocular irritation.[21] Acid Violet 43 **19** can be used in any cosmetic product because it showed no signs of significant toxicity.[23] Basic Blue 99 **20** is the most frequently used chemical product for hair tints.[13] HC

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Blue no. 2 **21** is exclusively used in hair dyes at a concentration of ≤1.7%.[25] Although this compound is mutagenic, no carcinogenic outcomes were observed in exposure studies with rats and mice.[25] Formulations containing HC Yellow no. 5 **22** are sold with a caution statement because of skin irritation. While some concern still exists, the available safety test data from the CIR expert panel demonstrated that HC Yellow no. 5 had no animal carcinogenicity as a hair dye ingredient at a concentration of ≤1.6%; the oral LD_{50} in rats is 555.56 mg/kg.[26] HC Red no. 7 has been confirmed as suitable for use in hair dyes by the CIR expert panel up to concentrations of 1% but may elicit skin irritation and mutagenicity (Table 2).[27]

3. HAIR DYE-INDUCED TOXICITIES AND ADVERSE HEALTH EFFECTS

3.1. Contact Allergy and Hair Loss. Hair dyeing-induced contact allergies occur frequently, which may further lead to the occurrence of ACD and urticarial contact (Table 3).[37−40] ACD commonly occurs on the scalp, face, and hands of hair dye users, manifesting as redness of the skin with vesiculation or scaling (Table 3),[41,42] which reduces quality of life in the affected individuals and can have negative socioeconomic impacts. The presence of contact allergies is closely attributed to the potent skin sensitizers contained in hair dyes, such as aromatic amines including PPD, a prevalent hair dye ingredient.[43] However, using permanent hair dyes containing PPD at concentrations ≤0.67% is unlikely to induce skin sensitization.[44] Recently, Goebel and co-workers[45] found that a methoxymethyl side chain introduced into PPD not only reduced the sensitizing intensity and the risk of allergic induction but also resulted in excellent hair coloring performance.

As far as plant-based hair dyes are concerned, although the public perceives them as safe, they can cause minor allergic reactions. For example, a small number of case reports have documented rare cases of ACD in users of plant-based hair dyes that contain pure henna, black tea, and indigo powder (Table 3).[46−48] There may be several explanations for this finding. First, pure henna, black tea, and indigo powder all contain about 15% tannins, large complex polyphenolic molecules that could cause the observed ACD. Although allergens in tannins have not been identified to date, the tannin-induced allergenic response is associated with inhibition of IL-8, IL-6, and TNF-α secretion from stimulated human mast cells.[49] The resulting color intensity that can be achieved by some plant colorants, such as pure henna, is time dependent.[47] Some darkening substances in proprietary formulas, such as lemon oil, vinegar, eucalyptus oil, or clove oil, may be added along with PPD to shorten the time of application.

As hairdressers are exposed on a regular basis to hair dyes in all steps of the dyeing process,[50] they face a significantly higher skin sensitization risk than personal hair dye users.[51,52] The use of protective gloves during hair coloring and warnings on the product labels that a sensitivity test is needed before application have decreased the incidence of hair dye-induced allergies. With sufficient protection against local and systemic exposure to oxidative hair dyes, hair coloring is unlikely to pose a serious risk to human health.[53,54] The adoption of adequate protective measures during the use of hair dye as well as appropriate education and training of hairdressers are crucial for lowering occupational risks and preventing hair dye-induced skin sensitization.[55]

Discoid lupus erythematosus (DLE) is an autoimmune skin disease that may be caused by ACD (Table 3); it is characterized by the development of autoantibodies that attack the skin at the interphase level.[56,57] Systemic lupus erythematosus (SLE) is another autoimmune disease manifesting multisystem disorders in addition to skin lesions. Although exposure to aromatic amines (such as PPD) may give rise to the occurrence of lupus, several studies collectively confirm an insignificant association between the use of hair dyes containing PPD and the increased risk of SLE.[58−60] Nevertheless, skin exposure to hair dyes may induce other severe but rare contact allergies, including neck and facial swelling and angioedema (Table 3).[61−63] Angioedema is a type I hypersensitivity reaction characterized by edema of the skin and subcutaneous tissues that damages the airways and gastrointestinal tract and may even lead to life-threatening laryngeal swelling.

Along with the increasing popularity of hair dye use, growing complaints about hair dye-induced hair loss have been a concern of dermatologists. Isik et al.[62] found that patients who experienced hair loss after hair dyeing presented symptoms of ACD before or at the time of hair loss, suggesting a close correlation between hair dye-induced ACD and hair loss (Table 3). H_2O_2, monoethanolamine, and PPD in hair dyes have been proposed as the main causative ingredients of hair dyeing-induced hair loss.[64,65] Based on histological examination conducted in animal tests, oxidative stress may be the mechanism underlying hair-dye induced dermatitis.[64,65] H_2O_2 and monoethanolamine, in particular, were shown to synergistically induce oxidative stress and cytotoxicity in human keratinocytes, an observation that is consistent with the histological data.[64,65]

3.2. Respiratory Sensitization, Allergies, And Other Diseases. Asthma and allergic rhinitis are common diseases that can result in overwhelmingly negative socioeconomic impacts.[66] Hairdressers are at a high risk of occupational rhinitis and asthma because, in daily work, they are frequently exposed to irritants and allergens such as persulfate and PPD in hair dyes.[67,68] A case-control study from Norway[69] showed that hairdressers over 40 years of age were more likely to suffer asthma-like symptoms than nonhairdressers due to their long occupational exposure to hair dye ingredients. Therefore, hairdressers and hairdressing apprentices should undergo continuous medical surveillance to monitor the risk factors and reduce the chance of respiratory diseases linked to occupational exposure.

3.3. Hair Dye Poisoning. Due to the easy availability and high toxicity of PPD, people in the developing world who want to commit suicide may attempt it by consuming this agent.[70] Hair dye poisoning may trigger the occurrence of some urgent and fatal outcomes, like pneumothorax, rhabdomyolysis, and acute kidney injury (AKI) (Table 3).[71−73] Orally ingesting PPD causes severe trauma to the airway and may lead to dyspnea, asphyxia, and other respiratory symptoms. If those ingesting PPD suffer respiratory distress and chest pain, then caution is needed regarding the occurrence of pneumothorax, which can be diagnosed by sonography or bedside X-ray. The pathological underpinning of rhabdomyolysis involves calcium ions leaking from the smooth endoplasmic reticulum, resulting in prolonged muscle contraction and irreversible changes in muscle structure.[74] The most striking laboratory characteristic

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Table 4. Studies Assessing the Association between Hair Dye Use and Carcinogenic Risk

study	study type	publication year	original nation	cases/controls	carcinogenic risk	association analysis	ref
Gago-Dominguez	case-control study	2001	USA	897/897	bladder cancer	2.1-fold (P = 0.04)	94
Kogevinas	case-control study	2006	Spain	152/166	bladder cancer	OR, 0.80 (0.50−1.50)	95
					bladder cancer	RR, 0.56 (0.32−0.99)	
					breast cancer	RR, 0.95 (0.83−1.05)	
Thun	epidemiologic study	1994	USA	NA	non-Hodgkin's lymphoma	RR, 0.95 (0.74−1.23)	96
					Hodgkin's lymphoma	RR, 0.55 (0.23−1.36)	
					multiple myeloma	RR, 1.05 (0.75−1.47)	
Henley	comment	2001	USA	NA	bladder cancer	RR, 1.08 (0.84−1.38)	97
Hartge	case-control study	1982	USA	2982/5782	bladder cancer	RR, 1.00 (0.90−1.20)	98
Ros	case-control study	2012	The Netherlands	1385/4754	bladder cancer	OR, 0.87 (0.65−1.18)	101
Koutros	case-control study	2011	USA	61/102	bladder cancer	OR, 3.30 (1.20−8.90)	105
Gago-Dominguez	case-control study	2003	USA	33/12[a]	bladder cancer	OR, 2.90 (1.20−7.50)	106
				37/17[a]	bladder cancer	OR, 2.50 (1.04−6.10)	94
Turati	meta-analysis	2014	Italy	3657/5962	bladder cancer	RR, 0.92 (0.77−1.09)	100
Boice	case-control study	1995	USA	528/2628	breast cancer	OR, 1.08 (0.87−1.30)	111
Koenig	case-control study	1991	USA	398/790	breast cancer	OR, 0.80 (0.60−1.10)	112
Cook	case-control study	1999	USA	315/393[b]	breast cancer	RR, 1.10 (0.90−1.30)	115
				204/138[b]	breast cancer	RR, 1.90 (1.40−2.50)	115
Zheng	case-control study	2002	USA	608/609	breast cancer	OR, 0.90 (0.70−1.20)	113
Nasca	case-control study	1992	USA	1617/1617	breast cancer	OR, 1.04 (0.90−1.21)	114
Heikkinen	case-control study	2015	Finland	6567/21598	breast cancer	OR, 1.23 (1.11−1.36)	116
Petro-Nustas	case-control study	2002	Jordan	100/100	breast cancer	OR, 8.62 (3.33−22.28)	117
Eberle	prospective study	2019	USA	NA	breast cancer	HR, 1.45 (1.10−1.90)	119
Nasca	case-control study	1980	USA	118/233	breast cancer	OR, 4.50 (1.20−15.78)	118
Gera	meta-analysis	2018	UK	NA	breast cancer	RR, 1.19 (1.03−1.37)	1
Xu	meta-analysis	2021	China	NA	breast cancer	OR, 1.07 (1.01−1.13)	120
					hematopoietic cancer	RR, 0.90 (0.70−1.20	
Grodstein	prospective study	1994	USA	NA	non-Hodgkin's lymphoma	RR, 1.10 (0.80−1.60)	136
					Hodgkin's lymphoma	RR, 0.90 (0.40−2.10)	
					multiple myeloma	RR, 0.40 (0.20−0.90)	
Miligi	case-control study	1999	Italy	165/828	Hodgkin's lymphoma	OR, 0.70 (0.50−1.10)	138
				134/828	multiple myeloma	OR, 0.80 (0.50−1.20)	
				260/828	leukemia	OR, 0.90 (0.70−1.30)	
Benavente	case-control study	2005	Spain	574/616	hematopoietic cancer	OR, 1.20 (0.90−1.70)	139
Tavani	case-control study	2005	Italy	446/1295	non-Hodgkin's lymphoma	OR, 1.03 (0.73−1.44)	142
				158/1295	Hodgkin's lymphoma	OR, 0.68 (0.40−1.18)	
				141/1295	multiple myeloma	OR, 1.17 (0.70−1.97)	
Wong	case-control study	2010	USA	649/1298	non-Hodgkin's lymphoma	OR, 0.93 (0.75−1.16)	147
				385/1432	non-Hodgkin's lymphoma	OR, 1.50 (1.10−2.20)	
Zahm	case-control study	1992	USA	70/1432	Hodgkin's lymphoma	OR, 1.70 (0.70−4.00)	148
				72/1432	multiple myeloma	OR, 1.80 (0.90−3.70)	
				56/1432	leukemia	OR, 1.00 (0.30−2.60)	
Zhang	case-control study	2009	USA	601/717	follicular lymphoma	OR, 1.90 (1.10−3.30)	149
					non-Hodgkin's lymphoma	OR, 1.30 (1.00−1.80)	150
Zhang	case-control study	2009	USA	4461/5799	non-Hodgkin's lymphoma	OR, 1.30 (1.10−1.40)	151
Guo	case-control study	2009	USA	261/247[c]	non-Hodgkin's lymphoma	OR, 1.46 (1.10−1.95)	152
				132/177[c]		OR, 1.03 (0.75−1.42)	
Cantor	case-control study	1988	USA	622/1245	non-Hodgkin's lymphoma	OR, 2.00 (1.30−3.00)	153
Herrinton	interview study	1994	USA	women	multiple myeloma	OR, 1.00 (0.70−1.40)	140
				men		OR, 1.50 (0.75−2.90)	
Koutros	case-control study	2009	USA	175/679	multiple myeloma	OR, 0.80 (0.50−1.10)	141
Mele	case-control study	1995	Italy	254/1161	leukemia	OR, 1.50 (0.60−3.70)	137
Cantor	case-control study	1988	USA	578/1245	leukemia	OR, 1.80 (1.10−2.70)	153
Chen	case-control study	2006	USA	272/418[d]	testicular germ cell tumor	OR, 1.50 (1.00−2.20)	163
				83/180[d]		OR, 1.70 (1.00−2.80)	
				189/238[d]		OR, 1.70 (1.10−2.60)	

[a]33/12 and 37/17 indicate subjects with the *NAT2* slow acetylation phenotype and those with the *CYP1A2* slow phenotype, respectively. [b]315/393 and 204/138 indicate subjects using the single hair dye method and those using two or more methods, respectively. [c]261/247 and 132/177 indicate subjects using hair dye before 1980 and those using hair dye in and after 1980, respectively. [d]272/418, 83/180, and 189/238 indicate all children, boys, and girls, respectively. Abbreviations: OR, odds ratio; RR, relative ratio; HR, hazard ratio.

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of rhabdomyolysis is a concentration of creatine phosphokinase in the plasma >10,000 U/L. If patients do not receive aggressive treatment, they will eventually die. Globally, approximately 13.3 million humans suffer from AKI per year, and more than 1 in 10 lose their life from this disease.[75] Individuals with AKI are also at a 9-fold risk of developing chronic kidney disease that can give rise to other organ dysfunctions. The characterized pathological manifestations of AKI include glomerular hyperemia, acute tubular necrosis, intratubular casts, and tubulointerstitial hemorrhages as well as mesangial hyperplasia. Hair dye-induced AKI occurs in a dose-dependent manner, but even with no intervention, the injured kidney may recover over time.[74]

3.4. Reproductive Toxicity and Disruption of Thyroid Hormone Synthesis. Zebrafish embryos are suitable animal models for studying how hair dyes affect embryonic growth. Two studies by Manjunatha et al.[76,77] demonstrated that exposure to hair dyes induced morphological and physiological abnormalities in zebrafish embryos, which provoked interest in determining whether hair dyes could affect human embryo development. Abnormal birth weight in humans (live birth weight <2500 g or >4000 g) reflects the poor health of the fetus and mother, which could contribute to the occurrence of obesity, malnutrition, hypertension, cardiovascular diseases, and cancer in the child in the future.[78] In terms of hair dyeing, the risk of infantile abnormal birth weight is elevated when mothers have irregular menstruation or have used hair dyes before pregnancy; the risk is increased if both factors exist.[79]

Resorcinol **28** is widely used as a component in hair dyes and cosmetics, and administration to rodents at high doses (>520 mg/kg/d) over 2 years disrupted thyroid hormone synthesis and caused goitrogenic effects.[80] Dermatological clinical reports indicated that frequent external application of ointments containing a high concentration of resorcinol (>34 mg/kg/d) to integrity-compromised human skin for several months to years can also induce thyroid side effects.[80] However, a risk assessment study concluded that under real-world conditions, exposure to resorcinol contained in hair dyes and cosmetics was unlikely to cause human thyroid dysfunction.[80]

4. ASSOCIATION BETWEEN HAIR DYE USE AND CANCER

4.1. Bladder Cancer. Bladder cancer is the most common urinary tract tumor and ranks 11th among the most common malignant tumors worldwide.[81,82] Occupational exposure to arylamines is frequently found in employees who engage in metal working, textile manufacture, driving, agriculture, construction, and rubber tire production and is the first identified cause of bladder cancer.[83] Hair dyes contain arylamines;[84] therefore, hairdressers and barbers are at risk of cancer from occupational exposure to arylamines. Findings demonstrate that individuals who pursue these occupations, particularly for longer than 10 years, experience a significantly increased risk of bladder cancer.[82,85,86] On the contrary, some epidemiologic studies observed no evidence of a causal association between occupational exposure to hair dyes and the increased risk for bladder cancer among male hairdressers.[87,88] Permanent hair dyes may contain *o*-phenylenediamine[89] **29** and 4-chloro-*o*-phenylenediamine **30** (Figure 1),[90] which have shown carcinogenicity in animal studies. These chemicals can lead to the formation of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) that is a marker of oxidative stress.[91] These findings indicate that the carcinogenicity of *o*-phenylenediamines is related to the generation of oxidative DNA damage, and 8-oxodG may be used as a biomarker to predict the associated carcinogenicity. Moreover, many permanent hair dyes contain 4-aminobiphenyl **31**, which is produced during the production of hair dyes where PPD is used as the primary intermediate.[92] Airoldi and colleagues found that 4-aminobiphenyl was a human bladder cancer carcinogen and was positively associated with tumor grade.[93] Thus, it is a public health concern to determine if other contaminants formed during hair dye production may constitute an additional health risk to hair dye users.

Currently available epidemiological data are controversial regarding whether hair dye use is a carcinogenic risk factor for bladder cancer. One population-based, case-controlled study found a positive association between the use of permanent hair dyes and enhanced bladder cancer risk,[94] while the results of other large-scale studies and a meta-analyses did not corroborate this conclusion (Table 4).[95−100] Studies investigating other confounding factors, like duration of use, frequency of use, age at first use, sex, and dye color, did not find a significant association between hair dye use and bladder cancer.[101−104] In addition, the New England Bladder Cancer Study[105] found no significant association between permanent hair dye use and increased bladder cancer risk in studies with female participants, but suggested that female users with a college degree had a greater risk of bladder cancer than nonusers (OR = 3.3; 95% CI, 1.2−8.9). This study also found that bladder cancer risk was higher among women with the *NAT2* slow acetylation phenotype compared to those with the *NAT2* rapid/intermediate acetylation phenotype (OR = 7.3; 95% CI, 1.6−32.6). A population-based study from the United States[106] involving 363 non-Asian women demonstrated a 2.9-fold increased risk of bladder cancer among women with the *NAT2* slow acetylation phenotype and a 2.5-fold increased risk among those with the *CYP1A2* slow phenotype who exclusively used permanent hair dyes, perhaps due to a slower detoxification capacity (Table 4). Significant positive frequency- and duration-related dose−response associations were reported in individuals with the *NAT2* and/or *CYP1A2* slow phenotypes. A follow-up study from Sweden[107] involving 38,866 female and 6824 male hairdressers and analyzing their malignancies over a period of 39 years demonstrated that the risk of bladder cancer among male hairdressers gradually decreased with follow-up time, albeit at the highest standardized incidence ratio (SIR) of 2.56 (95% confidence interval [CI], 1.36−4.39) in the 1960s. In recent decades, this risk has disappeared, with an SIR of 1.04 (95% CI, 0.74−1.40), suggesting that modern hair colorants do not exert an occupational bladder cancer risk in male hairdressers. However, there is another explanation for the nonapparent carcinogenic risk of bladder cancer from modern hair dyes: Aromatic amine-induced human urothelial cancers typically have a latency time longer than 20 years,[108] so the neoplastic onset time has not yet arrived. With the currently available data, bladder cancer risk due to exposure to hair dyes should be assessed on a case-by-case basis and the toxicological profile and individual exposure should be taken into consideration.

4.2. Breast Cancer. Breast cancer is one of the most common malignant tumors among women and the second leading cause of cancer death in the world.[109,110] The present evidence is inconclusive describing the link between personal hair dye use and breast cancer risk. Several epidemiological

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case-control studies[111−115] have indicated that hair dyeing does not increase the risk of breast cancer in women, even in those with benign breast diseases. In contrast, several case-control studies,[116−118] a prospective study,[119] and two meta-analyses[1,120] reported that personal hair dye use was related to the carcinogenic risk of breast cancer (Table 4). Early age at menarche is associated with an increased risk for breast cancer.[121] Each 2-year delay in onset of menstruation decreases this risk by approximately 10%.[122] The early exposure to menstruation and ovulation-associated hormones, linked with an earlier menstruation onset, has been proposed as an etiological factor for increased breast cancer risk.[123,124] Higher estrogen levels have been reported in individuals that experienced early menstruation onset, for several years after menarche.[125,126]

Endocrine disrupting chemicals (EDCs) are exogenous agents that interact with estrogen receptors or estrogen signaling pathways, disrupting the physiological function of the endocrine system and the development of the mammary tissue. This heterogeneous group of chemicals includes parabens, bisphenols, and phthalates, widely used substances in cosmetic and personal care products, and are present in hair dyes.[127,128] EDCs can be transported from the bloodstream to breast milk via passive diffusion and are then ingested by infants through breast-feeding. The hormone levels in the infants can be affected, and the growth of their germ cells can be disrupted.[129] Exposure to hair dyes containing EDCs in childhood may increase breast cancer risk, by lowering the age at menarche but most likely without affecting breast density.[130] Indeed, a study by Llanos et al.[131] demonstrated that the use of hair dyes containing EDCs is correlated with an elevated risk of estrogen receptor-positive breast cancer. Adolescent use of hair dyes containing EDCs may increase the risk of premenopausal breast cancer.[132] Di-*n*-butyl phthalate **32** is an EDC that is present in several hair dyes and personal-care products. In vitro studies revealed a large group of genes associated with fertility (inhibin, placental growth factor), the immune response (tumor necrosis factor-induced proteins), and antioxidant status (glutathione peroxidase) in normal human mammary epithelial cells were altered after exposure to di-*n*-butyl phthalate,[133] suggesting that these genes may be potential biomarkers for predicting reproductive problems associated with hair dye use.

The previously mentioned meta-analysis[120] concluded that the use of hair dyes, especially temporary and permanent hair dyes, increased breast cancer risk. However, an overall correlation between hair dyes and breast cancer risk as a function of race, timing of use, and dye color was not found. A case-control study from western Washington[115] found that young women using a single type of dyeing method (i.e., temporary, semipermanent or permanent dyes, straightener, and bleaching following dyeing or frosting) did not experience an increase in breast cancer risk (relative risk [RR] = 1.10; 95% CI, 0.90−1.30), but those who used two or more methods did have an increased risk (RR = 1.90; 95% CI, 1.40−2.50), indicating that reproductive-age women who used just one type of dyeing method avoided the increased risk of breast cancer (Table 4). These conflicting conclusions are likely explained by differences in individual subjects' molecular phenotypes, ages, and hair dyeing methods.

4.3. Hematopoietic Cancer. Hematopoietic cancers comprise a group of malignant tumors that occur in peripheral blood, bone marrow, and the lymphohematopoietic system, including leukemia, multiple myeloma (MM) and lymphoma. The etiology of some disorders is still unclear to date. Lymphomas originate from the lymphohematopoietic system and are classified into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) according to the lymphocyte type in the tumor tissues.

Although two population-based case-control studies determined[134,135] that hair dye use is a risk factor for primary myelodysplastic syndrome, a large number of studies have not identified a significant association between personal hair dye use and an overall increased risk of leukemia, HL, NHL, or MM (Table 4).[136−142] Because the data are conflicting regarding the potential carcinogenic effect of hair dye on the hematopoietic system, further studies should be performed to assess risk, for example, evaluating instances where hair dyes applied have very low concentrations of oxidative chemicals. If the duration of use is prolonged and the frequency of use is increased, the risk of hair dye-induced leukemia and other malignant lymphatic tumors is elevated.[96,143−145] Moreover, it was reported that the lymphoma risk of hair dye users compared to nonusers was elevated by 19%, and further increased by 26% when the frequency of use was >12 times per year.[142]

The incidence of NHL has increased globally in recent decades.[146] Occupational exposure to hair dyes may increase the risk of diffuse large B cell lymphoma, a subtype of NHL. A Shanghai hospital-based case-control study[147] revealed that personal hair dye use was not associated with an elevated risk of NHL or any NHL subtypes. In contrast, a population-based case-control study from the United States[148] showed a positive correlation between the use of permanent hair dyes and an increased risk of NHL, which became stronger for longer duration of use and earlier age of first use. Furthermore, several long-term case-control studies[149−153] found that hair dye use correlated with NHL risk and that this risk was significantly enhanced in users who dyed their hair prior to 1980, but not in those who used hair dyes in or after 1980 (Table 4). One possible explanation for this observation could be from the changes in hair dye formulation and the duration of use differences before and after 1980.

4.4. Maternal Hair Dyeing-Induced Childhood Tumors. As hair dyes contain EDCs, maternal hair dyeing during the month before pregnancy, during pregnancy, or during breastfeeding is considered a risk factor for offspring health. Childhood tumors are the second most common cause of childhood death in developed countries,[154] in which leukemia accounts for approximately 35.8% and ranks first.[155] Maternal hair dye use in the first trimester of pregnancy increases the risk of childhood acute lymphoblastic leukemia (ALL), and breastfeeding elevates the risk of childhood acute myeloid leukemia (AML). However, if children exhibited *MLL* (mixed lineage leukemia) gene rearrangements and their mothers were previously exposed to hair dye chemicals during pregnancy, an elevated risk of ALL or AML was not observed.[156] Gao and colleagues[157] found that the risk of maternal hair dyeing-induced childhood leukemia was reduced by breastfeeding, and if the breastfeeding duration reached 7−9 months, the reduction effect was more pronounced.

Neuroblastoma is the most common extracranial cancer in infants under the age of 12 months, corresponding to approximately 6−10% of global childhood tumors.[154] If hair dye use takes place a month before pregnancy or during pregnancy, the neuroblastoma risk in children is slightly

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increased, regardless of the type of hair dye used, and this effect was doubled by maternal semipermanent hair dye use.[158,159] Intriguingly, it was reported that mothers' use of temporary hair dye was linked to a greater neuroblastoma risk in children than maternal use of permanent hair dye.[154]

Testicular germ cell tumor (TGCT) is a rare human tumor with an estimated incidence of 8/100,000 and predominately occurs in males aged between 15 and 44 years.[160,161] Development of TGCTs is hypothesized to be due to a hormonal etiology related to EDCs. The United States Servicemen's Testicular Tumor Environmental and Endocrine Determinants study[162] indicated that pregnant women frequently using personal care products (e.g., face lotion) containing EDCs during their pregnancy or breast-feeding may increase the risk of TGCTs in their sons. Similarly, a study by Chen et al.[163] suggested that maternal hair dyeing during the month before pregnancy and during breastfeeding increased the risk of malignant germ cell tumors (MGCTs) in their sons and that breastfeeding also led to an elevated MGCT risk for their daughters (Table 4).[164,165,166]

5. CONCLUSIONS

Hair dyeing formulations are generally categorized into oxidative and nonoxidative types. Based on the safety assessment by the CIR expert panel and the FDA, a series of oxidative and nonoxidative chemicals have been assessed as safe for use in hair dyes, and an important aspect of this safety is based on the concentration of the compound(s) found in the hair dye. Personal or occupational exposure to hair dyes may still cause several kinds of toxicity and side effects, in which ACD is the most frequent with pneumothorax, rhabdomyolysis, and AKI being the most life-threatening. Although evidence in recent decades has not drawn a consistent conclusion about the correlation between hair dye use and risk of carcinogenesis, we cannot overlook that a positive association of hair dye use and cancer occurrence is reported in specific subpopulations. Moreover, maternal hair dyeing during the month before pregnancy, during pregnancy, or during breastfeeding is a risk factor for the occurrence of leukemia, brain tumors, and MGCTs in the offspring. An increasing body of studies indicates the need for ascertaining the association between hair dyeing and the carcinogenic risks in more specific subpopulations and investigating the molecular mechanism of hair dye chemical-induced toxicity and carcinogenicity. Overall, the association between personal hair dye use and cancer risk is likely to remain a debated topic. While the consensus opinion from the major cancer research centers suggests that there is not adequate evidence to link the practice of hair dyeing to cancer, several studies highlight hair dye-related toxicity and carcinogenicity as a public health concern. Given the amount of conflicting data, more in-depth chemical and systems toxicology studies are needed to better understand the risks associated with exposure to hair dyes and to address this important public health concern. Studies evaluating not only the risk of exposure to isolated hair dye ingredients but also to these compounds in the context of chemical mixtures will allow an assessment of the cumulative risk (exposure to multiple agents) and the interaction of exposures to multiple chemicals present in combination in hair dyes. Systems-based strategies, involving quantitative modeling, can shed light on the exposure-induced cellular and molecular alterations that might not be detected otherwise. It is anticipated that these current and emerging methods in toxicology can allow for a significantly superior assessment of complex mixtures such as hair dyes and therefore further support data-driven and fact-based evaluation of this public health concern.

AUTHOR INFORMATION

Corresponding Author

Weibin Zeng − *College of Animal Science and Technology, Shihezi University, Shihezi 832003 Xinjiang, China*; Phone: +86-18992898513; Email: zwbdky@126.com

Authors

Lin He − *Cancer Centre, Faculty of Health Sciences, University of Macau, Macau 999078 SAR, China*

Freideriki Michailidou − *Department of Health Sciences and Technology, ETH Zürich, 8092 Zürich, Switzerland; Collegium Helveticum, Institute for Advanced Studies (IAS) of the University of Zurich, ETH Zurich and Zurich University of the Arts, 8092 Zürich, Switzerland*

Hailey L. Gahlon − *Department of Health Sciences and Technology, ETH Zürich, 8092 Zürich, Switzerland*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.chemrestox.1c00427

Author Contributions

L.H. and F.M. contributed equally to this work. L.H. wrote the manuscript, collected data, and completed tables and figure drawing. F.M. and H.G. wrote and edited the manuscript and figures. W.E. was involved in the final approval of the manuscript. All authors reviewed and approved the manuscript prior to submission.

Notes

The authors declare no competing financial interest.

Search strategy and inclusion criteria: Peer-reviewed publications in English were searched in the PubMed, Web of Science, Scopus, Embase, and OVID databases using the search keyword "hair dye" during 1990−2021. All potential citations were retrieved prior to April 7, 2021. Eligible studies that evaluated hair dye ingredients, hair dye use-induced toxicity, and hair dye use-related cancers met the inclusion criteria.

Biographies

Dr. Lin He published 15 SCI papers as first or co-first author during the past five years. He is an oncologist in the Anhui Provincial Maternal and Child Health Hospital.

Dr. Freideriki Michailidou is a Collegium Research Fellow at ETH Zurich. Her current research encompasses biocatalysis and protein engineering, sustainable production, and safety assessment of fragrance ingredients.

Dr. Hailey Gahlon is a Group Leader in the Laboratory of Toxicology at ETH Zurich. Her current research focuses on understanding mechanisms of mitochondrial genome instability and strategies to circumvent anticancer drug resistance.

Dr. Weibin Zeng is the Group Leader of the College of Animal Science and Technology, Shihezi University. His current research centers on animal reproduction and biotechnology.

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