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Final Report on the Safety Assessment of 2-Chloro-*p*-Phenylenediamine and 2-Chloro-*p*-Phenylenediamine Sulfate

ABSTRACT

2-Chloro-*p*-Phenylenediamine and 2-Chloro-*p*-Phenylenediamine Sulfate are colorants used in hair dyes at concentrations less than 1.0%. In an oral subchronic toxicity test using rats and mice, all male rats and one female rat died in the 1% concentration of 2-Chloro-*p*-Phenylenediamine dose group; at 0.3%, no rats or mice died but the mean body weight gain was depressed. In the mice, one of the males and none of the females died in the 1% dose group. In a test for ocular irritation, 2.5% 2-Chloro-*p*-Phenylenediamine produced, at most, only mild conjunctival inflammation. 2-Chloro-*p*-Phenylenediamine was not a sensitizer when assayed on abraded and intact skin. The cited chronic studies do not provide sufficient evidence to conclude that the compound was carcinogenic in either mice or rats. Epidemiological studies, both prospective and retrospective, support this conclusion. On the basis of the data presented in the report, it is concluded that 2-Chloro-*p*-Phenylenediamine and 2-Chloro-*p*-Phenylenediamine Sulfate are safe as a "coal tar" hair dye ingredient at the current concentrations of use.

INTRODUCTION

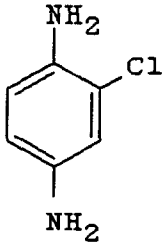
2-CHLORO-*P*-PHENYLENEDIAMINE and 2-Chloro-*p*-Phenylenediamine sulfate are hair colorants used exclusively in hair dyes. The following is a summary of data available to CIR concerning the chemistry, cosmetic use, subchronic oral toxicity, and carcinogenicity of these compounds.

CHEMISTRY

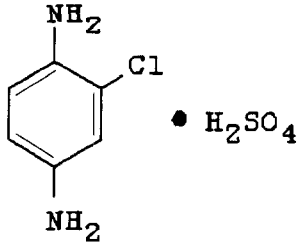
Definition and Structure

2-Chloro-*p*-Phenylenediamine (CAS# 615-66-7) and 2-Chloro-*p*-Phenylenedia-

mine Sulfate (CAS# 6219-71-2) are classified as halogenated aromaticamines that conform to the following formula (Estrin et al., 1982):



2-Chloro-*p*-Phenylenediamine



2-Chloro-*p*-Phenylenediamine Sulfate

Other names for these compounds include 2-chloro-1,4-benzenediamine (sulfate) and 2-chloro-4-aminoaniline (sulfate). The color index number for 2-Chloro-*p*-Phenylenediamine is 76065; 2-Chloro-*p*-Phenylenediamine Sulfate, #76066 (Society of Dyers and Colorists, 1971).

Chemical and Physical Properties

2-Chloro-*p*-Phenylenediamine, molecular weight 142.5, has a melting point of 64°C (Society of Dyers and Colorists, 1971). The sulfate form has a reported melting range of 251–253°C (NCI, 1978) and is soluble in alcohol and water (Society of Dyers and Colorists, 1971). Manufacturer-grade 2-Chloro-*p*-Phenylenediamine Sulfate was analyzed for identity and purity. Elemental analysis results were in agreement with the molecular formula $ClC_6H_3(NH_2)_2\ H_2SO_4$. The melting range was 250–262°C (NCI, 1978). The UV absorption maxima are 288, 238, and 206 (CTFA, 1991). Thin-layer chromatography tests in two different solvent systems, visualized with ultraviolet light and furfural, indicated the presence of a number of motile and non-motile impurities. Impurities were also detectable by high-pressure liquid chromatography. The result of vapor-phase chromatography was one homogeneous peak (NCI, 1978).

COSMETIC USE

The only reported use of 2-Chloro-*p*-Phenylenediamine and its sulfate salt is in permanent hair dyes (CTFA; 1991; Nikitakis, 1988). Data submitted to the Food and Drug Administration (FDA) in 1984 by cosmetic firms participating in the voluntary cosmetic registration program indicated that 2-Chloro-*p*-Phenylenediamine was used in only one formulation for hair dyes and colors at a concentration up to 0.1%. The sulfate salt was used in 61 hair dyes and colors: 25 products with a concentration of 0.1–1%; 36 products, less than 0.1% (see Table 1) (FDA, 1984).

Voluntary filing of product formulation data with FDA by cosmetic manufacturers and formulators conforms to the prescribed format of present concentration ranges and product categories as described in Title 21, Part 720.4 of the Code of Federal Regulations (21 CFR 720.4). Because data are only submitted within the framework of preset concentration ranges, opportunity exists for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a

concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to tenfold error in the assumed ingredient concentration. Some cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, and, therefore, the value reported by the cosmetic manufacturer or formulator may not necessarily reflect the actual concentration of the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA.

Hair-coloring formulations containing 2-Chloro-*p*-Phenylenediamine and its salt are applied to or may come in contact with hair, skin (particularly the scalp), and eyes. Individuals dyeing their hair may use such formulations as often as once a week. Hairdressers may come in contact with products containing these compounds several times a day.

Semipermanent hair dyes are usually applied in a shampoo base and contain thickeners, alkalizers, and foam stabilizers. Permanent hair dyes contain couplers and an oxidant in addition to the primary intermediate (the actual dye). Users may be exposed to reactive intermediates as well as to unreacted dyes (Corbett and Menkart, 1973).

The oxidative or permanent hair dyes containing the 2-Chloro-*p*-Phenylenediamine or its salt, as "coal tar" hair dye products (Elder, 1985a), are exempt from the principal adulteration provision and from the color additive provision in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act of 1938 when the label bears a caution statement and "patch test" instructions for determining whether the product causes skin irritation (Federal Register, 1979). In order to be exempt, the following caution statement must be displayed on all coal tar hair dye products:

> Caution—this product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.

Instructions call for a 24-h patch on the skin of the user with the intermediates and hydrogen peroxide mixed in the same manner as in use. This test is to be performed prior to each and every application of the hair dye (Corbett and Menkart, 1973).

TABLE 1. PRODUCT FORMULATION DATA

	Total no. of formulations in category	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*		
			>1–5	*>0.1–1*	*≤0.1*
2-Chloro-*p*-Phenylenediamine Hair dyes/colors (requiring a cautionary statement)	811	1	0	0	1
2-Chloro-*p*-Phenylenediamine Sulfate Hair dyes/colors (requiring a cautionary statement)	811	61	0	25	36

Source: FDA, 1984.

At its February 11, 1992 meeting, the CIR Expert Panel issued the following policy statement on coal tar hair dye product labeling:

> The Cosmetic Ingredient Review Expert Panel has reviewed the cosmetic industry's current coal tar hair dye product labeling, which recommends that an open patch test be applied and evaluated by the beautician and/or consumer for sensitization 24 h after application of the test material and prior to the use of a hair dye formulation.
>
> Since the recommendation on the industry's adopted labeling establishes a procedure for individual user safety testing, it is most important that the recommended procedure be consistent with current medical practice.
>
> There is a general consensus among dermatologists that screening of patients for sensitization (allergic contact dermatitis) should be conducted by the procedures used by the North American Contact Dermatitis Group and the International Contact Dermatitis Group.[1,2,3] Basically, these procedures state that the test material should be applied at an acceptable concentration to the patient, covered with an appropriate occlusive patch, and evaluated for sensitization at 48 and 72 h after application. The CIR Expert Panel has cited the results of studies conducted by both the North American Contact Dermatitis Group and the International Contact Dermatitis Group in its safety evaluation reports on cosmetic ingredients.[4]
>
> During the August 26–27, 1991 public meeting of the CIR Expert Panel, all members agreed that the cosmetics industry should change its recommendation for the evaluation of the open patch test from 24 h to 48 h after application of the test material.
>
> The industry was advised of this recommendation and asked to provide any compelling reasons why this recommendation should not be made by the Expert Panel and adopted by the cosmetics industry. No opposition to this recommendation was received. At the February 11, 1992 public meeting of the CIR Expert Panel, this policy statement was adopted.

2-Chloro-*p*-Phenylenediamine Sulfate appears on the list of approved substances for cosmetic use in Japan with the proviso that the ingredient must be identified on the product container (CTFA, 1980). The European Economic Community (EEC) Cosmetic Directive Update (1988), does not list 2-Chloro-*p*-Phenylenediamines as prohibited substances for cosmetics.

ANIMAL TOXICOLOGY

Subchronic Oral Toxicity

Fischer 344 rats and B6C3F$_1$ mice were used to study the subchronic toxicity of 2-Chloro-*p*-Phenylenediamine Sulfate. Animals were divided into 6 groups of each

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[1]North American Contact Dermatitis Group. 1980. Patch testing in allergic contact dermatitis. American Academy of Dermatology.

[2]Eiermann et al. 1982. Prospective study of cosmetic reactions. J. Am. Acad. Dermatol. **6**:909–917.

[3]Adams et al. 1985. A five-year study of cosmetic reactions. J. Am. Acad. Dermatol. **12**:1062–1069.

[4]Elder 1985. Final report on the safety assessment of p-Phenylenediamine. J. Am. Coll. Toxicol. **4**(3):203–266.

species; five males and five females per group. Concentrations of 0.03, 0.1, 0.3, 1.0, and 3.0% of test material were incorporated into the feed and administered to the animals for 8 wk. A control group was given untreated feed. At the end of the treatment period, survivors were killed and necropsied. Results for rats and mice receiving 3.0% 2-Chloro-*p*-Phenylenediamine Sulfate were not reported. At 1.0%, 5 male rats and 1 female rat died; at 0.3%, no deaths occurred, but mean body weight was depressed 10.4% in males and 6.4% in females. In mice, there was one death in the 1.0% male group and none in the female group. Mean body weights were depressed 3.8% in males and 14.4% in females. A concentration of 0.3% resulted in no deaths in either sex and no mean weight depression in males; a 16.1% mean weight depression was reported in females (NCI, 1978).

Ocular Irritation

A solution of 2.5% w/v 2-Chloro-*p*-Phenylenediamine in water buffered with 0.05% sodium sulfite (pH 7) was instilled into one eye of each of three rabbits. Ten seconds after instillation, the eyes were rinsed with 20 ml of distilled water. One animal had mild conjunctival inflammation. The other two animals had no observable reaction to the test substance (CTFA, 1991).

Primary Dermal Irritation

Three albino rabbits were clipped free of hair. A patch with 0.5 ml of 2.5% w/v 2-chloro-*p*-phenylenediamine in distilled water was applied to both one abraded and one intact site on each animal. After 24 hours of exposure, the patches were removed and the test sites scored on a scale of 0 to 4 (CFR, Title 16, Section 1500.41). Sites were scored again 72 h after the application. There was no observed reaction to the test substance throughout the study (CTFA, 1991).

Sensitization

The sensitization potential of 2-Chloro-*p*-Phenylenediamine was examined using the maximization test of Magnusson and Kligman. Fifteen female Pirbright white guinea pigs received 5 intracutaneous injections (amount not stated) of 0.3% 2-Chloro-*p*-Phenylenediamine in distilled water over a period of 5 days. Ten female Pirbright white guinea pigs, which received no injections, served as controls. This was followed by a 4-wk nontreatment period. Animals were then patch tested with 0.003, 0.006, 0.03, and 0.3% 2-Chloro-*p*-Phenylenediamine, and their reactions were scored after 24 and 48 h. A Student's *t*-test was used to compare the skin reaction scores of the test and control animals. 2-Chloro-*p*-Phenylenediamine was strongly sensitizing (CTFA, 1991).

CARCINOGENICITY

NCI (1978) performed an oral chronic test in Fischer 344 rats and B6C3F$_1$ mice to determine the carcinogenicity of commercial 2-Chloro-*p*-Phenylenediamine Sulfate. Animals were weighed just prior to the experiment, twice weekly for the first 12 wk, and then monthly until the end of the study. Animals were checked twice daily for mortality and moribund animals were killed and necropsied. Feed consumption was monitored

monthly. Palpations were done monthly. All of the remaining animals were killed for necrospy. Gross and microscopic histological examinations were performed on a variety of tissues and lesions.

Rats were divided into three groups. The low- and high-dose groups consisted of 50 animals of each sex and were fed diets with concentrations of 0.15% and 0.3% 2-Chloro-*p*-Phenylenediamine Sulfate, respectively. The control group contained 20 rats of each sex. The treatment period was 107 weeks, during which time the treated animals were continuously supplied with treated feed. Adequate numbers of both male and female rats survived to the end of the test period in order to study late-developing neoplasms. Clinical abnormalities observed were: alopecia in 1 low and 1 high-dose females; eye irritation in 2 low-dose males, 1 high-dose male, 4 low-dose females, and 2 high-dose females; subcutaneous masses in 2 low-dose males, 3 high-dose males, 2 control females, 4 low-dose females, and 2 high-dose females; abdominal distention in 1 high-dose male; and general pallor in 1 low-dose female. Mean body weight and mortality were not effected by the compound. Neoplastic and nonneoplastic lesions in treated rats were considered not significantly different than controls. The only compound-related effect was an increase in the incidence of transitional-cell hyperplasia of the renal pelvis (see Table 2). The increase in transitional-cell hyperplasia of the renal pelvis was dose related in males, but not in females. A small number of transitional-cell neoplasms were also found in dosed rats. These effects alone were not considered by NCI to be sufficient evidence for the carcinogenicity of 2-Chloro-*p*-Phenylenediamine sulfate in Fischer 344 rats (NCI, 1978).

Mice were divided into three groups. The low- and high-dose groups consisted of 50 animals of each sex and were fed diets with concentrations of 0.3% and 0.6% 2-Chloro-*p*-Phenylenediamine Sulfate, respectively. The control group contained 20

Table 2. Transitional-Cell Hyperplasia and Neoplasms in Rats; Hepatocellular Lesions in Mice

	Males			*Females*		
	Control	*0.15%*	*0.3%*	*Control*	*0.15%*	*0.3%*
Fischer 344 Rats						
Renal Pelvis						
No. of animals with kidneys examined	20	49	50	20	48	49
Transitional cell hyperplasia	0	17 (35%)	30 (60%)	0	14 (29%)	8 (16%)
Transitional cell carcinoma	0	1	0	0	0	0
Urinary Bladder						
No. of animals with urinary bladders examined	18	48	47	20	48	48
Transitional cell papilloma	0	1	0	0	0	0
Transitional cell carcinoma	0	0	1	0	1	0
B6C3F1 Mice						
Hepatocellular Lesions						
No. of animals with livers examined	17	49	46	19	49	44
Focal hyperplasia	0	1	1	0	1	1
Hepatocellular adenoma	0	4 (8%)	10 (22%)	0	3 (6%)	5 (11%)
Hepatocellular carcinoma	4 (24%)	8 (16%)	10 (22%)	2 (11%)	2 (4%)	4 (9%)

Source: NCI, 1978.

mice of each sex. The treatment period was 104 weeks for the low dose group, during which mice were continuously supplied with test diet. The high dose group received treated feed for 87 weeks, followed by 18 weeks of untreated feed. Controls were monitored for 107 weeks. Mortality in the female, but not the male, treated groups was affected by the compound. Adequate numbers of both male and female mice survived to the end of the test period to assess late-developing neoplasms. Mean body weights were slightly depressed for both male and female mice. Clinical abnormalities observed were: alopecia in 15 control males, 48 low-dose males, 24 high-dose males, 11 control females, 6 low-dose females, and 8 high-dose females; eye irritation in 1 low-dose male, 1 high-dose male, 1 control female, and 1 high-dose female; subcutaneous masses in 1 high-dose male and 2 control females; abdominal masses in 1 control male, 2 control females, and 3 low-dose females. Both sexes of treated mice had a dose-related increase of hepatocellular adenomas and carcinomas as compared to controls (see Table 2). Fisher exact tests performed on these data, however, did not support the association of these lesions with the test compound. Other neoplastic and nonneoplastic lesions in treated mice were considered not significantly different than controls. NCI (1987) concluded that 2-Chloro-*p*-Phenylenediamine Sulfate was associated with dose-related increases in hepatocellular lesions in $B6C3F_1$ male mice.

The International Agency for Research on Cancer (IARC) (1987) considered the evidence as inadequate for 2-Chloro-*p*-Phenylenediamine to be an animal carcinogen.

EPIDEMIOLOGY

Approximately 40% of American women dye their hair, often at monthly intervals over a period of years (Corbett and Menkart, 1973). The U.S. EPA reported that [approximately] 15 million people are potentially exposed to hair dye ingredients as a result of personal use or in the application of hair dyes to other people (47 FR 979).

A variety of published studies have assessed the association between occupational exposure to and use of hair dyes and the risk of cancer. These studies do not note which specific hair dye ingredients were involved in the human exposure. A summary of reports of how occupational exposure to hair dye affects the risk of bladder cancer (Cole et al., 1972; Anthony and Thomas, 1970; Dunham et al., 1968; Wynder et al., 1963) and lung cancer (Garfinkel et al., 1977; Menck et al., 1977), or use of hair dyes affects the risk of bladder cancer in men or women (Jain et al., 1977) and breast cancer in women (Wynder and Goodman, 1983; Hennekens et al., 1979; Shore et al., 1979; Nasca et al., 1979; Kinlen et al., 1977; Shafer and Shafer, 1976) has been published in previous Cosmetic Ingredient Review reports on *p*-Phenylenediamine, 2-Nitro-*p*-Phenylenediamine, and 4-Nitro-*o*-Phenylenediamine (Elder, 1985a,b). In the small case-controlled study by Shore et al. (1979), a positive correlation between hair dye and breast cancer was reported. When their study was extended to include 398 breast cancer cases, the same investigators could not implicate hair dye use as an important cause of human breast cancer (Koenig et al., 1991). The latter study indicated that beauticians who work for five or more years in this occupation have an increased breast cancer risk. However, the increased risk was not a strong finding, and "if beauticians are at increased breast cancer risk, exposures other than hair dyes may be responsible" (Koenig et al., 1991).

An epidemiology prospective study involving 118,404 U.S. women concluded that the use of permanent hair dyes appears unlikely to cause any important increase in the risk of breast cancer (Green et al., 1987).

Evidence of any carcinogenic effect from hair dyes investigated among the occupations and users examined is insufficient (Clemmesen, 1981). Clemmesen (1981) discussed the difficulties implicit in epidemiologic studies and reviewed many of the papers that investigated the relationship of the risk of cancer to occupational exposure to or use of hair dyes. He concluded that most researchers used samples that were too small to allow conclusions and that analyses of duration and intensity of exposure, lag time, and the influence of lifestyle factors, such as tobacco use, were deficient in many cases.

SUMMARY

The oxidative or permanent hair dyes containing 2-Chloro-p-Phenylenediamine and 2-Chloro-*p*-Phenylendiamine sulfate, as "coal tar" hair dye products, are exempt from the principal adulteration provision and from the color additive provision in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act of 1938 when the label bears a caution statement and appropriate "patch test" instructions for determining whether the product causes skin irritation. The patch test, in which the intermediates and hydrogen peroxide are mixed in the same manner as in use, is to be performed prior to each and every application of the hair dye.

In an oral subchronic toxicity test, 2-Chloro-*p*-Phenylenediamine Sulfate was incorporated into the feed of Fischer 344 rats and B6C3F_1 mice. In the rats, all of the males and one of the females died in the 1% concentration dose group. At 0.3%, no rats died but the mean body weight gain was depressed 10.4% in males and 6.4% in females. In the mice, one of the males and none of the females died in the 1% dose group. Mean body weight was depressed 3.8% in males and 14.4% in females. No mice died in the 0.3% dose group, but mean body weight was depressed 16.1% in females.

In a test for ocular irritation, 2.5% 2-Chloro-*p*-Phenylenediamine was instilled into one eye each of three rabbits. One animal had mild conjunctival inflammation, the other two had no reaction.

Three albino rabbits had no reaction to 0.5 ml of 2.5% 2-Chloro-*p*-Phenylenediamine in a patch test on abraded and intact skin. 2-Chloro-*p*-Phenylenediamine was found to be strongly sensitizing in a maximization test. In an oral chronic test, Fischer 344 rats and B6C3F_1 mice were fed 2-Chloro-*p*-Phenylenediamine Sulfate for up to 107 weeks. The compound was associated with dose-related increases in hepatocellular adenomas in B6C3F_1 mice. NCI and IARC concluded, however, that there was insufficient evidence that the compound was carcinogenic in either mice or rats.

DISCUSSION

The CIR Expert Panel recognizes that 2-Chloro-*p*-Phenylenediamine has been shown to be a strong sensitizer in guinea pigs using the Magnusson and Kligman maximization test. Hair dyes containing 2-Chloro-*p*-Phenylenediamine and 2-Chloro-*p*-Phenylenediamine Sulfate are exempt from the principal adulteration provision and from the color additive provisions in sections 601 and 706 of the Federal Food, Drug and Cosmetic Act of 1938 when cautionary statements and patch test instructions are conspicuously displayed on the labels. Prophetic patch test of hair dye formulations

with open patches is less predictive of skin reactions than patch testing with closed patches. False negative reactions may occur. Some persons may be sensitized even under the proper conditions of use.

CONCLUSION

On the basis of the data presented in this report, the CIR Expert Panel concludes that 2-Chloro-*p*-Phenylenediamine and 2-Chloro-*p*-Phenylenediamine Sulfate are safe as "coal tar" hair dye ingredients at the current concentrations of use.

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