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Cancer and Coal Tar Hair Dyes: An Unregulated Hazard to Consumers. HRD-78-22; B-164031(2). December 6, 1977. 20 pp.

Report to Rep. John E. Moss, Chairman, House Committee on Interstate and Foreign Commerce: Oversight and Investigations Subcommittee; by Elmer B. Staats, Comptroller General.

Issue Area: Consumer and Worker Protection: Identification of Hazardous Consumer Products (909).

Contact: Human Resources Div.

Budget Function: Health: Prevention and Control of Health Problems (553).

Organization Concerned: Department of Health, Education, and Welfare; Food and Drug Administration: Div. of Cosmetics Technology; National Institutes of Health: National Cancer Inst.; National Inst. for Occupational Safety and Health; Cosmetic, Toiletry, and Fragrance Association.

Congressional Relevance: House Committee on Interstate and Foreign Commerce: Oversight and Investigations Subcommittee.

Authority: Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301 et seq.). P.L. 86-618. 28 C.F.R. 6439. 36 C.F.R. 16902. Toilet Goods Association v. Finch (419 F.2d 21 (1969)).

About 33 million women use hair dyes to temporarily or permanently change their hair color. Most dyes marketed for use by women are known as coal tar hair dyes because initially coal tar was the only commercially practical source of material needed to synthesize the colors used in them. Most coal tar hair dyes contain colors derived from petroleum rather than coal tar. Because a color chemically identical to the petroleum-derived color could be derived from coal tar, the Food and Drug Administration (FDA) classifies petroleum-derived colors as coal tar colors and regulates hair dyes containing them accordingly. Coal tar hair dyes whose labeling contains a prescribed statutory warning concerning possible skin irritation and blindness are exempt from Federal Food, Drug, and Cosmetic Act provisions concerning adulteration, but they are not exempt from misbranding provisions of the act. Findings/Conclusions: Exemptions in the act do not permit FDA to regulate coal tar hair dye products effectively; they bar the agency from banning or restricting the use of cancer-causing coal tar hair dyes. Although coal tar hair dyes are subject to FDA labeling requirements, the agency has not used this authority to require a cancer warning on labels of dyes containing known human or animal carcinogens. Colors known to cause or suspected of causing cancer reportedly are being used in all three types of coal tar hair dyes. Data indicate that the cancer-causing coal tar hair colors may be absorbed through the skin and scalp. Colors that may be used in some temporary and semipermanent hair dyes are derived from benzidine, a known carcinogen; they may be

a significant cancer risk because the colors may break down to benzidine in the human body. Nine color additives banned for use in cosmetics other than coal tar hair dyes are listed in the Cosmetic Ingredient Dictionary as available for use in coal tar hair dyes. Recommendations: The Secretary of Health, Education, and Welfare should direct the FDA Commissioner to evaluate safety data on coal tar hair dye ingredients and require, where applicable, a cancer or other appropriate warning on product labels. The Congress should permit FDA to better regulate coal tar hair dyes by repealing exemptions in section 601(a) and 601(e) of the Food, Drug, and Cosmetic Act. (Author/SW)

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04296



REPORT OF THE COMPTROLLER GENERAL OF THE UNITED STATES

Cancer And Coal Tar Hair Dyes: An Unregulated Hazard To Consumers

Some coal tar hair dyes may pose a significant risk of cancer to consumers because they contain colors known to cause or suspected of causing cancer in humans or animals. Colors that may be used in some temporary and semipermanent hair dyes are derived from benzidine, a known human carcinogen, and may break down to benzidine in the body. Other colors suspected of causing cancer are used in temporary, semipermanent, and permanent coal tar hair dyes.

However, exemptions granted to coal tar hair dyes under the Federal Food, Drug, and Cosmetic Act prevent the Food and Drug Administration from regulating hair dyes effectively. The exemptions bar the agency from banning or restricting the use of coal tar hair dyes containing cancer-causing colors, if their labeling warns of possible skin irritation or blindness. The Congress should repeal these exemptions.



COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

B-164031(2)

The Honorable John E. Moss, Chairman
Subcommittee on Oversight and
Investigations
Committee on Interstate and Foreign
Commerce
House of Representatives

Dear Mr. Chairman:

This is in response to your letter of October 19, 1977, requesting information on coal tar derivative hair dyes. The information in this report was developed as part of our review of the Food and Drug Administration's regulation of cosmetics and will also be included in our report to the Congress on the results of that review.

The Food and Drug Administration is part of the Department of Health, Education, and Welfare. As you requested, we did not seek formal Department comments on the report. However, we did discuss the report's contents with Food and Drug Administration officials and we considered their views in preparing the report. The Department will be afforded an opportunity to offer written comments on our report to the Congress on cosmetics.

As agreed with your office, no further distribution of this report will be made before 30 days unless you publicly announce its contents earlier.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "James R. Stacks".

Comptroller General
of the United States

COMPTROLLER GENERAL'S REPORT
TO THE HONORABLE JOHN E. MOSS
HOUSE OF REPRESENTATIVES

CANCER AND COAL TAR HAIR DYES:
AN UNREGULATED HAZARD
TO CONSUMERS

D I G E S T

About 33 million women use hair dyes to temporarily or permanently change their hair color. There is increasing evidence that some colors used in coal tar hair dyes--the dyes most widely used--may carry a significant risk of cancer to users.

Cosmetics, including hair dyes, are regulated under the Federal Food, Drug, and Cosmetic Act.

Exemptions in the act do not permit the Food and Drug Administration to regulate coal tar hair dye products effectively; they bar the agency from banning or restricting the use of cancer-causing coal tar hair dyes.

The Congress should repeal these exemptions. If that is done, colors used in these dyes will be subject, similar to other color additives, to premarket approval by the Food and Drug Administration for safety. Manufacturers will have to prove the safety of these colors.

Although coal tar hair dyes are subject to Food and Drug Administration labeling requirements, the agency has not used this authority to require a cancer warning on labels of coal tar hair dyes containing known human or animal carcinogens.

The Secretary of Health, Education, and Welfare should direct the Commissioner of the Food and Drug Administration to evaluate safety data on coal tar hair dye ingredients and require, where applicable, a cancer or other appropriate warning statement on product labels.

Tear Sheet. Upon removal, the report cover date should be noted hereon

Coal tar hair dyes are divided into three groups--temporary, semipermanent, and permanent--depending on the type of coal tar color used, the method used to apply the dye, and the permanence of the color.

--Temporary hair dyes are rinses, removable with one shampooing.

--Semipermanent hair dyes usually are applied in a liquid base and are left on the hair for 20 to 40 minutes before being rinsed out; they wear off after several shampoos.

--Permanent hair dyes, accounting for about \$3 out of every \$4 spent on hair dyes, produce color only after they are oxidized inside the hair fiber by hydrogen peroxide or another oxidant; they are not readily removed by shampooing.

Generally, a cosmetic is considered adulterated if it contains any poisonous or deleterious substance.

Coal tar hair dyes whose labeling contains a prescribed statutory warning concerning possible skin irritation and blindness are exempt from these provisions. In addition, a cosmetic is considered adulterated if it contains a color additive not approved for safety by the Food and Drug Administration under the color additive provisions of the act. Again, however, coal tar hair dyes are exempted.

A cosmetic is considered misbranded if its labeling is false or misleading. Coal tar hair dyes are not exempt from the misbranding provisions.

Colors known to cause or suspected of causing cancer reportedly are being used in all three types of coal tar hair dyes. Data indicates that the cancer-causing coal tar hair colors may be absorbed through the skin and scalp. (See p. 4.)

Colors that may be used in some temporary and semipermanent hair dyes are derived from benzidine, a known carcinogen; they may be a significant cancer risk because the colors may break down to benzidine in the human body.

Benzidine was identified as a human carcinogen in the 1930s. Many scientists believe that cancer can result from ingestion, inhalation, or skin absorption of benzidine.

The Cosmetic, Toiletry, and Fragrance Association, an industry trade group, lists eight coal tar colors derived from benzidine in the second edition of its Cosmetic Ingredient Dictionary. Hair dye manufacturers voluntarily reported to the Food and Drug Administration the use of these dyes in 26 coal tar hair dye products. Because many cosmetic manufacturers do not report their product formulations to the Food and Drug Administration, the total number of products containing the benzidine-derived colors has not been determined.

Nine color additives banned for use in cosmetics other than coal tar hair dyes are listed in the Cosmetic Ingredient Dictionary as available for use in coal tar hair dyes.

Colors of this type normally are used in temporary hair dyes. Hair dye manufacturers voluntarily reported the use of these colors in 21 hair dye products. Four of the 9 colors--known as FD&C Green No. 2, FD&C Red No. 2, FD&C Violet No. 1, and FD&C Red No. 1--have been found to cause cancer in animals.

Eleven other colors identified in animal tests as suspected carcinogens are listed in the Cosmetic Ingredient Dictionary as available for use in coal tar hair dyes.

GAO could not readily identify individual products that contain the 11 colors. Generally, such colors would be used in temporary or semipermanent hair dyes.

Screening tests and animal-feeding studies provide evidence that some widely used permanent hair dye ingredients may be carcinogenic or mutagenic.

University of California researchers tested 169 marketed permanent hair dyes using a sensitive and simple bacterial screening test and found that 150 were mutagenic and possibly carcinogenic. They found also that 9 of 18 ingredients used in permanent hair dyes were mutagenic.

The bacterial test is believed to offer strong evidence of carcinogenicity but, according to the Food and Drug Administration, does not alone provide sufficient evidence to conclude that a substance is harmful to humans.

Animal-feeding studies are being conducted on a number of permanent hair dye ingredients for the National Cancer Institute. Although analysis of the studies has not been completed, the Institute advised the Food and Drug Administration on October 18, 1977, that two of the ingredients--toluene-2,4-diamine and 2,4-diaminoanisole sulfate--were carcinogenic in animals.

Hair dye manufacturers have reported to the Food and Drug Administration the use of toluene-2,4-diamine in 7 hair dyes and the use of 2,4-diaminoanisole or its sulfate salt in 407 hair dyes.

The Cosmetic, Toiletry, and Fragrance Association has questioned the appropriateness of screening tests and feeding studies for determining the safety of hair dye products. It cites five skin-painting studies in which a hair dye was applied to the skin

of the test animal with no adverse effects to demonstrate the safety of toluene-2,4-diamine and 2,4-diaminoanisole.

Although skin-painting studies more closely approximate the actual conditions of hair dye use, some researchers have questioned the adequacy of the studies performed.

As requested by the Subcommittee, GAO did not obtain written comments from the Food and Drug Administration. However, GAO has considered the views of the Food and Drug Administration in preparing this report.

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ABBREVIATIONS

CTFA	Cosmetic, Toiletry, and Fragrance Association
EDF	Environmental Defense Fund
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act, as amended
HEW	Department of Health, Education, and Welfare
NCI	National Cancer Institute
NIOSH	National Institute of Occupational Safety and Health

CHAPTER 1

INTRODUCTION

According to a representative of the Cosmetic, Toiletry, and Fragrance Association (CTFA), an industry trade association, about 33 million women use hair dyes to temporarily or permanently change their hair color. Most dyes marketed for use by women are known as coal tar hair dyes because initially coal tar was the only commercially practical source of material needed to synthesize the colors used in them. The remainder of the women's hair dye market is divided between metallic dyes, which are advertised to gradually cover gray hair, and vegetable dyes, such as henna, which are natural dyes. Although some men use coal tar hair dyes, the most popular dyes marketed for men are metallic dyes. Estimates on the number of men who use hair dyes were not readily available.

The Deputy Director of the Food and Drug Administration's (FDA's) Division of Cosmetics Technology told us that most coal tar hair dyes contain colors derived from petroleum rather than coal tar. Because a color chemically identical to the petroleum-derived color could be derived from coal tar, FDA classifies petroleum-derived colors as coal tar colors and regulates hair dyes containing them accordingly. Throughout this report we refer to all hair dyes containing petroleum-derived and coal-tar-derived colors as coal tar hair dyes.

TYPES OF COAL TAR HAIR DYES

Coal tar hair dyes are divided into three groups--temporary, semipermanent, and permanent--depending on the type of coal tar color used, the method used to apply the dye, and the permanence of the color.

Temporary hair dyes are rinses which add highlights and brightness to natural color, improve shades of gray hair, and blend unevenly colored hair. The first rinses were introduced in 1922 and were patterned after a similar product used to color curtains and other textiles. Commercial products generally contain a mixture of several colors to obtain a given shade. Temporary dyes are usually applied to the base of the hair and are combed through to the tip. The dyes are deposited on the surface of the hair fiber. Because they do not generally penetrate the hair, they are completely removable with one shampooing.

Semipermanent hair dyes penetrate the hair but wear off after several shampoos. They are often used to blend streaked hair, to improve the coloring of white or gray hair, or to add highlights to naturally blond hair. Semipermanent dyes are usually applied in a liquid base which is left on the hair for 20 to 40 minutes before being rinsed out. Because no chemical reaction takes place during application, semipermanent dyes do not significantly affect the structure and the color of hair as do permanent hair dyes. Like temporary hair dyes, semipermanent dyes generally contain a blend of several colors to obtain the desired shade.

Permanent, or oxidation, hair dyes account for about \$3 out of every \$4 spent on hair dyes. Such dyes work through a series of chemical reactions. The coal tar ingredients in permanent hair dyes are mostly colorless "intermediates" which produce color only after they are oxidized inside the hair fiber by hydrogen peroxide or another oxidant ^{1/}. Permanent hair dyes produce fast colors that are not readily removed by shampooing. Subsequent dyeing, perhaps monthly, is required to color new hair growth and restore the color of previously dyed hair.

REGULATION OF HAIR DYES

Cosmetics, including hair dyes, are regulated under the Federal Food, Drug, and Cosmetic Act, as amended (FD&C Act) (21 U.S.C. 301 et seq.). Generally, cosmetics are considered adulterated if they contain any poisonous or deleterious substance and are considered misbranded if their labeling is false or misleading. However, coal tar hair dyes that conform to statutory labeling requirements are exempt from the adulteration provisions of the act.

Problems in regulating coal tar hair dyes under existing legislation are discussed in chapter 3.

^{1/}The primary intermediates, such as para-phenylenediamine and para-aminophenol, are oxidized by hydrogen peroxide or another oxidant. The resulting products react with a coupler, such as 2,4-diaminoanisole, resorcinol, meta-aminophenol, and 1,5-dihydroxynaphthalene, or with another unoxidized "para" dye to give the desired shade.

SCOPE OF REVIEW

We reviewed legislation, regulations, and practices relating to FDA's regulation of cosmetics, including coal tar hair dyes; examined FDA's records on coal tar hair dyes; and reviewed reports of scientific studies on the safety of coal tar hair dyes. We also interviewed officials from FDA and the Department of Health, Education, and Welfare's (HEW's) National Cancer Institute.

CHAPTER 2

SOME COAL TAR HAIR DYES MAY POSE

CANCER RISK TO CONSUMERS

There is increasing evidence that some coal tar hair dyes may pose a significant risk of cancer to users because known or suspected cancer-causing colors in these dyes may be absorbed through the skin and scalp. Specifically:

- Temporary hair dyes may contain coal tar colors shown to cause cancer in laboratory animals and banned by FDA for use in other cosmetic products.
- Temporary and semipermanent hair dyes may contain azo colors 1/ derived from benzidine, a known human carcinogen. Such colors contain benzidine as a contaminant, and some of the colors may breakdown in the body and release benzidine.
- Other coal tar colors available for use in temporary or semipermanent hair dyes have reportedly caused cancer in laboratory animals.
- Evidence from screening tests or animal studies indicate that several coal tar colors used in permanent hair dyes, including toluene-2,4-diamine and 2,4-diaminoanisole 2/ may cause cancer.

Existing epidemiological studies provide limited and conflicting evidence about the incidence of cancer among coal tar hair dye users.

SKIN ABSORPTION

Several studies have demonstrated that coal tar hair dye ingredients are absorbed through the skin and scalp.

1/Azo colors contain an "azo" group--two connected nitrogen atoms, each of which is usually linked to a carbon atom.

2/2,4-diaminoanisole is commonly referred to as 4-methoxy-m-phenylenediamine on hair dye labels.

In a study published in 1968 1/ three permanent hair dye ingredients--p-phenylenediamine, m-phenylenediamine, and toluene-2,5-diamine--were applied to the skin of dogs in gels and fluids, such as those used in hair dyes. The amount of dye absorbed was calculated from the concentrations found in the blood or the urine. About 1 percent of the p-phenylenediamine applied was absorbed in 3 hours. The amount absorbed increased to about 7 percent if the gel was covered with aluminum foil immediately after application. Absorption decreased to about 0.1 percent if the dye was mixed with hydrogen peroxide before application. About 3 and 4 percent, respectively, were absorbed after applying toluene-2,5-diamine and m-phenylenediamine.

A second study 2/ demonstrated the absorption of toluene-2,5-diamine through human skin. The hair of five persons was dyed with a dye composed of toluene-2,5-diamine, resorcinol, and hydrogen peroxide. About 0.3 percent of the toluene-2,5-diamine was absorbed.

In a 1975 study report 3/, University of California researchers noted that many aromatic amines and diamines, such as benzidine, are absorbed through human skin. They estimated that women could absorb as much as 1 percent of the hair dye chemicals applied to the scalp.

FDA has received several reports of consumers experiencing brown or discolored urine following use of hair dyes. Although we identified several reports stating that the colors in semipermanent hair dyes are absorbed, we could not find any studies identifying the extent to which they are absorbed.

1/Kiese, M., Rachor, M., and Rauscher, E., "The Absorption of Some Phenylenediamines Through the Skin of Dogs," Toxicology and Applied Pharmacology, vol. 12, pp. 495-507, 1968.

2/Kiese, M., and Rauscher, E., "The Absorption of p-Toluenediamine [toluene-2,5-diamine] Through Human Skin in Hair Dyeing," Toxicology and Applied Pharmacology, vol. 13, pp. 325-331, 1968.

3/Ames, B., Kammen, H.O., and Yamasaki, E., "Hair Dyes Are Mutagenic: Identification of a Variety of Mutagenic Ingredients," Proceedings of the National Academy of Sciences of the United States of America, vol. 72, no. 6., pp. 2423-2427, June 1975.

BANNED COLORS USED IN HAIR DYES

Only color additives permanently or provisionally listed by FDA as safe can be legally used in food, drugs, or cosmetics other than coal tar hair dyes. Coal tar hair dyes are exempt from the color additive provisions of the FD&C Act and, therefore, coal tar color additives banned from use in food, drugs, or other cosmetics may continue to be used in coal tar hair dyes. (See ch. 3.)

Nine color additives banned for use in cosmetics are listed in the second edition of the CTFA Cosmetic Ingredient Dictionary 1/ as available for use in coal tar hair dyes. According to FDA officials, such colors would generally be used in temporary hair dyes. We found evidence that four of the nine colors--FD&C Green No. 2, FD&C Red No. 2, FD&C Violet No. 1, and FD&C Red No. 1--cause cancer in laboratory animals. The dictionary refers to these colors as Acid Green 5, Acid Red 27, Acid Violet 49, and HC Red No. 6, respectively. The remaining five colors (and their CTFA references) are: External D&C Red No. 11 (Acid Red 1), External D&C Red No. 13 (Acid Red 73), External D&C Red No. 8 (Acid Red 88), External D&C Yellow No. 3 (Acid Yellow 11), and External D&C Blue No. 1 (Basic Blue 9). We did not identify the toxic effects associated with these colors.

From data submitted by cosmetic manufacturers under FDA's voluntary program for filing cosmetic product ingredient statements 2/, we identified four hair dyes containing FD&C Red No. 2, four containing FD&C Red No. 1, and thirteen containing External D&C Blue No. 1. Because of the limited participation in the voluntary program, the total number of products containing the nine colors could not be determined.

1/The dictionary was prepared by CTFA based on data supplied by the cosmetic industry on the ingredients being used or promoted for use in cosmetic products. The second edition was issued in 1977.

2/FDA lacks authority to require cosmetic manufacturers to submit data on the ingredients used in their products. The voluntary program was established in 1972, but participation has been limited.

BENZIDINE-DERIVED AZO COLORS

Among the coal tar colors that may be used in temporary and semipermanent hair dyes are several azo colors derived from benzidine. According to the Environmental Protection Agency, benzidine-derived azo colors may contain up to 20 parts per million of benzidine. More significant, however, are data indicating that some of the benzidine-derived azo colors may reconvert to benzidine in the body.

Benzidine was identified as a human carcinogen in the 1930s when factory workers exposed to benzidine developed an increased incidence of bladder cancer. Many scientists believe that cancer can result from ingestion, inhalation or skin absorption of benzidine. In animal studies benzidine caused liver tumors in mice, rats, and hamsters and bladder cancer in dogs.

In a study report published in July 1975 ^{1/}, two researchers from the New York University Medical Center reported on the metabolic reduction of benzidine-derived azo colors in the rhesus monkey. Monkeys were fed by stomach tube a single dose of benzidine or a benzidine-derived azo color dissolved in dimethyl sulfoxide. Four benzidine-derived azo colors were included in the study. Control urine was collected from each monkey before the test was begun.

The researchers analyzed urine collected from the monkeys over a 72-hour period and found benzidine and a benzidine metabolite (monoacetyl benzidine) in extracts of urine from both the monkeys fed benzidine and those fed benzidine-derived azo colors. They found that the metabolic reduction of the colors to benzidine was nearly total.

The researchers stated that the results of their work support the implication of an earlier study (1973) that an increased incidence of bladder cancer found in Japanese silk kimono painters resulted from benzidine metabolically derived from ingested azo colors. The earlier study had demonstrated the reduction of benzidine-derived azo colors to benzidine in the presence of certain bacteria.

^{1/}Rinde, E., and Troll, W., "Metabolic Reduction of Benzidine Azo Dyes to Benzidine in the Rhesus Monkey," Journal of the National Cancer Institute, vol. 55, no. 1, pp. 181-182, July 1975.

HEW's National Institute of Occupational Safety and Health (NIOSH) began a study in 1977 to determine the degree of occupational risk to workers in the textile-dyeing and leather-tanning industries exposed to benzidine-derived colors. NIOSH notes that most dyestuffs are of a chemical class which offers the potential for rapid skin and lung absorption but that it is not known if the metabolites resulting from such occupational exposure differ from those reported in the New York University study.

We could not locate any studies on the extent to which benzidine-derived azo colors are absorbed through the skin.

The CTFA Cosmetic Ingredient Dictionary lists eight benzidine-derived azo colors as available for use in coal tar hair dyes. From data submitted to FDA by cosmetic manufacturers under its voluntary program for filing cosmetic product ingredient statements, we identified, as shown in the following table, 26 hair dye products that contained benzidine-derived azo colors.

<u>Benzidine-derived azo color</u>	<u>Number of hair dye products containing color</u>
Direct Black 38	7
Direct Black 131	4
Direct Blue 6	1
Direct Brown 1	2
Direct Brown 1:2	2
Direct Brown 2	6
Direct Brown 31	4
Direct Brown 154	-
	<u>26</u>

All of the identified products were temporary rinses. FDA officials told us, however, that benzidine-derived colors may also be used in semipermanent hair dyes. Because of the limited participation in the voluntary program, the total number of products containing the eight benzidine-derived azo colors could not be determined.

Two of the eight colors were included in the New York University study, and one of them--Direct Black 38--also reportedly was used by the Japanese kimono painters who developed an increased incidence of cancer.

The university researchers concluded that

"It is not our intent to imply that all azo dyes are biologically [sic] reduced to carcinogens, but those derived from carcinogenic aromatic amines should receive particular attention."

The CTFA dictionary lists other azo colors derived from toluene-2,4-diamine, toluene-2,4-diamine sulfate, and o-tolidine, each of which is a known or a suspected animal carcinogen.

OTHER SUSPECTED CARCINOGENS IN TEMPORARY AND SEMIPERMANENT HAIR DYES

Eleven other colors listed as suspected carcinogens in the 1976 NIOSH Registry of Toxic Effects of Chemical Substances were listed in the CTFA Cosmetic Ingredient Dictionary as available for use in coal tar hair dyes. The NIOSH registry lists the studies upon which the list is based. Neither we nor NIOSH, however, have reviewed the adequacy of the studies or the appropriateness of the studies as a basis for determining the safety of the colors for use in hair dyes.

The table below lists the 11 colors, the animal species in which the study was made, and the route by which the color was administered to the animal.

<u>Color</u>	<u>Test animal</u>	<u>Route of administration</u>
Acid Blue 9	Rat	Subcutaneous
	Rat	Parenteral
Acid Blue 9 ammonium salt	Rat	Subcutaneous
	Rat	Parenteral
Acid Blue 74	Rat	Subcutaneous
Acid Red 18	Rat	Oral
Acid Red 87	Rat	Subcutaneous
Acid Yellow 73 sodium salt	Rat	Subcutaneous
Basic Orange 2	Mouse	Oral
Basic Violet 10	Rat	Subcutaneous
Disperse Yellow 3	a/Not identified	Not identified
Pigment Red 53	a/Not identified	Not identified
Pigment Red 53:1	a/Not identified	Not identified

a/Reviewed by the World Health Organization's International Agency for Research on Cancer. Available data were indefinite with respect to carcinogenicity.

Although the CTFA dictionary indicated that these colors are available for use in coal tar hair dyes, we were not readily able to identify individual products that contain the 11 colors.

POSSIBLE CARCINOGENICITY OF PERMANENT HAIR DYES

Screening tests and animal-feeding studies provide additional evidence that some widely used permanent hair dye ingredients may be carcinogenic or mutagenic. CTFA has questioned the appropriateness of such studies for determining the safety of hair dye products and has cited certain animal-skin-painting studies to support the safety of these products. However, some scientists have questioned the adequacy of the studies cited by CTFA to establish the safety of coal tar hair dyes.

We reviewed some of the more significant studies, which are briefly discussed below.

Screening tests

University of California researchers have developed a very sensitive and simple bacterial screening test for detecting chemical mutagens. The test is also believed to offer strong evidence of possible carcinogenicity. The researchers reported that 85 percent of the chemicals found carcinogenic in animal studies were detected as mutagens in the bacterial test. By contrast, less than 10 percent of the chemicals classified as noncarcinogenic in animal studies showed mutagenic potential in the bacterial tests.

The researchers subjected 169 marketed permanent hair dyes to the bacterial test. The dyes were tested both before and after mixing with hydrogen peroxide. Of the 169 dyes tested, 150 (89 percent) were found to be mutagenic. Most of the dyes retained their mutagenic activity after mixing with hydrogen peroxide. The researchers also tested 25 semi-permanent type hair dyes and found most to be mutagenic.

In addition, the researchers obtained from industry representatives 18 chemicals used in permanent hair dyes and tested them for mutagenic properties. Nine of the 18 showed

various degrees of mutagenicity 1/. Oxidation by hydrogen peroxide caused three of the chemicals to become strongly mutagenic.

According to an official from FDA's Division of Cosmetics Technology, although screening tests offer strong indications of possible carcinogenicity and mutagenicity, they alone do not provide sufficient evidence to conclude that a substance is harmful to humans. The official stated that such tests need corroboration by tests on animals.

National Cancer Institute studies

The National Cancer Institute (NCI) has initiated animal studies on the carcinogenicity of 16 coal tar hair dye ingredients. The studies, which were being performed by contractors, involve feeding the dye ingredients to rats and mice or applying the dye ingredient to the skin of rabbits and mice.

As of October 1977 NCI had not completed the analysis of any of the studies. According to an NCI official, the completion of NCI's analysis of many of the studies has been delayed by higher priority work involving pesticides and industrial solvents. NCI's Associate Director for Carcinogenesis Testing Program said, however, that because of the structural similarity of the coal tar colors being tested to known carcinogens, he expects many of them to be found carcinogenic. He said that analysis probably would not be completed before the spring of 1978.

On September 2, 1977, the FDA Commissioner wrote to the NCI Director requesting that priority be given to completion of the evaluations of 2,4-diaminoanisole, toluene-2,4-diamine, and any other ingredients which show positive effects. The letter stated:

1/The nine ingredients were: 2,4-diaminoanisole, 4-nitro-o-phenylenediamine, 2-nitro-p-phenylenediamine, 2,5-diaminoanisole, 2-amino-5-nitrophenol, m-phenylenediamine, o-phenylenediamine, 2-amino-4-nitrophenol, and toluene-2,5-diamine.

"Possible positive results with respect to two of the compounds studied, in particular, 2,4-diaminoanisole (2,4 DAA) and toluene-2,4-diamine (2,4 TDA) 1/ have attracted our attention. In addition, there is evidence that compounds such as these do penetrate intact skin.

"In light of this and the extensive use of hair dyes * * * the need to confirm the conclusions suggested by preliminary reviews in an orderly scientific manner is obvious."

By letter dated October 18, 1977, NCI's Associate Director for Carcinogenesis Testing Program advised the FDA Commissioner that NCI had found both 2,4-diaminoanisole and toluene-2,4-diamine carcinogenic in animals. The Associate Director gave FDA a draft of a technical report on 2,4-diaminoanisole and advised FDA that results of the other study would be submitted to the "Journal of the National Cancer Institute" for publication.

By letter dated October 21, 1977, the Acting Director of FDA's Bureau of Foods notified NCI that FDA was beginning an immediate evaluation of the draft technical report on 2,4-diaminoanisole.

On October 17, 1977, the Environmental Defense Fund, Inc. (EDF), a private nonprofit national consumer organization, petitioned FDA to require all hair dye products containing 2,4-diaminoanisole or 2,4-diaminoanisole sulfate to bear a cancer warning label. EDF stated that its evaluation of the data on 2,4-diaminoanisole compiled, but not yet released by NCI, showed the dye to be carcinogenic in both rats and mice following oral ingestion. EDF noted that the dye caused a statistically significant increase in certain types of tumors in male and female rats and mice.

2,4-diaminoanisole is a basic component of most permanent hair dyes. We identified, from data submitted by manufacturers to FDA, 407 hair dye products containing 2,4-diaminoanisole or 2,4-diaminoanisole sulfate.

1/Most cosmetic manufacturers stopped using toluene-2,4-diamine in hair dyes after it was found to cause cancer in laboratory animals. However, data submitted to FDA under its voluntary program for filing cosmetic product ingredient statements indicates that it is still used in at least seven permanent hair dye products.

Skin-painting studies

Skin-painting studies involve applying a chemical or a chemical mixture to the skin of the test animal. Because topical application more closely approximates the actual conditions of hair dye use and permits testing the actual mixture of compounds produced during oxidation, CTFA believes that only skin-painting studies can offer meaningful results on hair dye carcinogenicity.

CTFA noted that 2,4-diaminoanisole and toluene-2,4-diamine had been included in five skin-painting studies in which no problems had been found. While some researchers recognize the usefulness of skin-painting studies, they have questioned the adequacy of the studies performed. Two of these studies are discussed below.

Study 1 ^{1/} involved the twice weekly application of toluene-2,5-diamine, either alone in a vehicle (a carboxymethylcellulose gel) or in a mixture with two other hair dye ingredients (resorcinol and 2,4-diaminoanisole) to the shaved dorsal skin of Sprague-Dawley rats for 2 years. Two control groups were used; one group was treated with the vehicle only and the other group remained untreated. No positive control group was used (i.e., no group received a known carcinogen). All rats surviving the 2-year application period were observed for another 6 months.

The researchers reported:

- There was no evidence that the hair dye ingredients caused any adverse effects.
- There was no difference between the control and treated rats with respect to lifespan or the type and the incidence of tumors.
- There were no tumors or other skin reactions at the site of application.
- Histopathological studies of the liver, kidney, and lungs provided no evidence of degenerative change or functional disturbance.

^{1/}Kinkel, H. J., and Holzmann, S., "Study of Long-term Percutaneous Toxicity and Carcinogenicity of Hair Dyes (Oxidizing Dyes) in Rats," Food Cosmetic Toxicology, vol. 11, pp. 641-648, Pergamon Press, 1973.

However, University of California researchers questioned the usefulness of the study in evaluating the safety of hair dyes, because of the small number of animals and low dosages used in the study. They noted that experiment could not detect a chemical that increased the incidence of cancer in the population by 5 percent.

Study 2 1/ involved applying one of three different hair dye formulations 2/ to the skin of mice. Each formulation, and a control formulation without a dye intermediate, was administered, after mixing with hydrogen peroxide, to two groups of mice--one weekly and one every 2 weeks for 18 months. A positive control group and an untreated control group were also used.

The researchers reported that no evidence of toxicity or carcinogenicity had been noted. They noted that one ingredient used in the tests, toluene-2,4-diamine, had previously been shown to cause liver cancer when fed to rats.

The University of California researchers, however, believed that this study was also inadequate for evaluating safety for humans. They noted that, compared to the previous study, smaller doses had been used, the dyeings occurred weekly or every 2 weeks rather than twice a week, and the animals had been sacrificed after only 18 months.

EPIDEMIOLOGICAL STUDIES

Epidemiology is a science that deals with the incidence, distribution, and control of disease in a given population. Epidemiological studies compare the incidence of a disease, such as bladder cancer, in a population exposed to a particular chemical to the incidence of the disease in an unexposed population in order to identify causes for the disease. The two populations should be closely matched according to such factors as age, sex, and smoking habits.

1/Burnett, C., Lanman, B., Giovacchini, R., Wolcott, G., Scala, R., and Keplinger, M., "Long-Term Toxicity Studies on Oxidation Hair Dyes," Food Cosmetic Toxicology, vol. 13, pp. 353-357, Pergamon Press, 1975.

2/Each formulation contained oleic acid, isopropanol, sodium sulphite, ammonia, toluene-2,5-diamine sulphate, p-phenylenediamine, resorcinol, and deionized water. In addition, each formulation contained one of the following: toluene-2,4-diamine base, 2,4-diaminoanisole sulphate, or m-phenylenediamine base.

Although extensive epidemiological studies have not been performed for users of coal tar hair dyes, two studies on breast cancer patients have been performed with conflicting results. However, deficiencies have been noted in both studies.

In one study 1/ a New York physician compared the use of coal tar hair dyes among his women breast cancer patients to use of the dyes by women of the same age who did not have breast cancer. The study showed that 87 of 100 breast cancer patients had been longtime (over 5 years) users of coal tar hair dyes whereas only 26 percent of the women without breast cancer were longtime users. The women were apparently matched by age, but not by other factors which could affect the incidence of cancer, such as smoking habits.

In the second study 2/ 191 women with breast cancer and 561 women without breast cancer were matched according to age, marital status, and social class. Although data on factors known to affect the incidence of breast cancer was obtained from the women, the women were not matched according to those factors. The study showed no relationship between breast cancer and use of hair dyes.

According to the October 17, 1977, EDF petition to FDA, the second study is inadequate because of the short followup period. EDF maintains that the latent period for development of cancer after exposure to hair dye use will probably be over 15 years, but too few women in the study had used hair dyes for more than 14 or 15 years before cancer diagnosis to make the data useful.

1/Shafer, N., and Shafer, R. W., "Potential of Carcinogenic Effects of Hair Dyes," New York State Journal of Medicine, March 1976, pp. 394-396.

2/Kinlen, L. J., Harris, R., Garrod, A., and Rodriguez, K., "Use of Hair Dyes by Patients with Breast Cancer: A Case Control Study," British Medical Journal, 1977, vol. 2, pp. 366-368.

CHAPTER 3

NEED TO REPEAL HAIR DYE EXEMPTIONS

Although coal tar hair dyes expose consumers to potentially serious hazards, FDA cannot effectively regulate them because it lacks adequate legislative authority. The FD&C Act requires cosmetics to be properly labeled and to be unadulterated. However, coal tar hair dyes whose labeling contains a prescribed statutory warning concerning possible skin irritation and blindness are exempt from the adulteration provisions of the act. Because the labeling of most such dyes bears the statutory warning, they are generally exempt from FDA regulation under the adulteration provisions even if they pose hazards, such as cancer, not covered by the statutory warning.

COAL TAR HAIR DYE EXEMPTIONS

Section 601(a) of the act states that a cosmetic shall be deemed to be adulterated if it bears or contains any poisonous or deleterious substance that may render it injurious to users under normal use. It further states, however, that:

"* * * this provision shall not apply to coal-tar hair dye, the label of which bears the following legend conspicuously displayed thereon: 'Caution--This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should first be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.', and the labeling of which bears adequate directions for such preliminary testing."

According to the November 1974 issue of the FDA Consumer, an agency periodical, the coal tar hair dye exemption was granted because industry persuasively argued that while the dyes could not meet safety standards of the FD&C Act, they should nonetheless be sold to meet popular demand.

Since July 12, 1960, the Color Additive Amendments to the FD&C Act (Public Law 86-618) have required the establishment of regulations listing color additives that are safe for use in food, drugs, and cosmetics. Under these

amendments, FDA must approve a color additive for safety before its use in cosmetics is permitted. However, coal tar hair dyes were granted an exemption from the color additive provisions of the FD&C Act. Under section 601(e), a cosmetic is considered adulterated:

"If it is not a hair dye and it is, or it bears or contains, a color additive which is unsafe within the meaning of section 706(a)."

The U.S. Court of Appeals, Second Circuit, ruled in the 1969 case of Toilet Goods Association v. Finch (419 F. 2d 21 (1969)) that the above exemption does not apply to coloring ingredients in hair dyes not derived from coal tar, such as the metallic and vegetable dyes. The court noted that the legislative history of the Color Additive Amendments contained no indication that the Congress intended to broaden the 601(a) exemption.

Under section 602 a cosmetic is considered misbranded if its labeling is false or misleading in any particular. Coal tar hair dyes are not exempt from the misbranding provisions of the act.

EXEMPTIONS HINDER EFFECTIVE REGULATION

Many coal tar hair dye products contain ingredients that have been shown to cause cancer in humans or animals. Ordinarily FDA could ban the use of such ingredients in a cosmetic product under the adulteration provisions of the act, if the substance may cause cancer under the conditions of use of the cosmetic. Because of the exemption, however, FDA cannot ban the use of a cancer-causing coal tar hair dye even if the evidence suggests that the dye is a human carcinogen, such as a hair dye containing a benzidine-derived azo color.

In recognition of this problem, FDA in 1963 issued regulations defining the conditions under which the exemption applied. The regulation excluded from the exemption any coal tar hair dyes which posed a hazard that was different from those covered by the statutory warning (28 F.R. 6439, June 22, 1963). According to the regulation,

"If the poisonous or deleterious substance in the 'hair dye' is one to which the caution is inapplicable and for which patch-testing provides no safeguard, the exemption does not apply * * *

A patch test is a test on the forearm, on the bend of the elbow, or behind the ear to detect allergic sensitivity.

However, in the 1969 case the U.S. Court of Appeals upheld a district court ruling (278 F. Supp. 786) invalidating that portion of the regulation. The court of appeals found that

"The Government's argument should indeed be appealing to a legislator--what good is the warning to make a patch test if the test will not disclose the danger? But a court must take the statute as it is, and Congress wrote with great specificity. Whether it relied solely on the patch test warning because it was unaware in 1938 that coal-tar dyes might have damaging effects not detectable by such a test, as the Government asserts but the industry denies, or because it thought such instances so rare as not to warrant indentation of the exemption, the language is too clear for us to read it as meaning something different from what it so plainly says, at least in the absence of persuasive legislative history." (419 F. 2d 21, 29 (1969))

Thus the court ruled that even if a coal tar hair dye were found to cause cancer or some other adverse effect which would not be detected by a patch test, the dye could not be removed from the market under the adulteration provisions of the FD&C Act if the products' labeling bore the statutory warning. In 1971 FDA revised the regulation to delete the objectionable statement (36 F.R. 16902, Aug. 26, 1971).

In the opinion of an FDA attorney, FDA could probably require under the misbranding provisions of the act that an additional warning be placed on the labeling of coal tar hair dyes posing hazards under conditions of use, such as cancer not covered by the statutory warnings.

However, because section 601(e) exempts coal tar hair dyes from the color additives provisions of the act, FDA cannot require the manufacturers of these hair dyes to prove the safety of their products under the color additive requirements, and, therefore, FDA has the burden of proof for any additional label warnings it may require. By contrast, FDA can require the manufacturers of colors used in metallic and vegetable hair dyes to prove the safety of their colors

because the law does not similarly exempt these hair dye products from the color additive requirements.

In its October 17, 1977, petition to FDA, EDF asked the agency to require the following warning on labels of coal tar hair dyes containing 2,4-diaminoanisole.

"This product contains the chemical 2,4 DAA [2,4-diaminoanisole], which can enter your bloodstream through your scalp and has been shown to cause cancer in animals."

FDA is considering this matter. As of October 31, 1977, FDA had not responded to the petition or taken action to require cancer warning labels on other coal tar hair dyes containing known animal carcinogens, such as toluene-2,4-diamine and FD&C Red No. 2.

CONCLUSIONS

Many coal tar hair dyes contain known or suspected carcinogens that pose a potential hazard to the consumer because they may be absorbed through the skin and scalp. However, the exemptions in the FD&C Act do not permit FDA to effectively regulate coal tar hair dye products in that they bar FDA from banning or restricting the use of coal tar hair dyes that may cause cancer under the conditions of use.

Although coal tar hair dyes are subject to FDA labeling requirements, the agency has not used this authority to require a cancer warning on labels of coal tar hair dyes containing known human or animal carcinogens. The issuance of such regulations is made difficult by the fact that the burden of proof for their need rests with FDA, rather than the manufacturers. If the coal tar hair dye exemptions were repealed, the color ingredients used in these dyes would be subject, similar to other color additives, to premarket approval by FDA for safety and manufacturers would have to prove the safety of the colors.

In February 1974 testimony before the Subcommittee on Health, Senate Committee on Labor and Public Welfare, FDA supported the elimination of the exemptions. FDA testified that:

"coal tar hair dyes should not receive privileged treatment but should be subject to the same regulation and safety appraisal as other cosmetics."

Therefore, to strengthen regulation of coal tar hair dyes and to provide a greater measure of protection to users, the exemptions should be repealed.

RECOMMENDATION TO THE SECRETARY, HEW

We recommend that the Secretary, HEW, direct the FDA Commissioner to evaluate safety data on coal tar hair dye ingredients and require, where applicable, a cancer or other appropriate warning on product labels.

RECOMMENDATION TO THE CONGRESS

To permit FDA to better regulate coal tar hair dyes, we recommend that the Congress repeal exemptions in sections 601(a) and 601(e) of the FD&C Act concerning these dyes.