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Final Report on the Safety Assessment of HC Red #3

ABSTRACT

HC Red #3, also known as N1(2-hydroxyethyl)-2-nitro-*p*-phenylenediamine, is a colorant used in semipermanent hair dyes. Unidentified nitrosamines were found in two lots of HC Red #3, at concentrations of 20 ± 5 ppm and 11 ± 8 ppm. The LD_{50} for HC Red #3 was >500 mg/kg in mice and >1000 mg/kg in rats. In a subchronic feeding study, the mean body weights of male mice and rats were reduced. Other than a pigmentation of the urine and some organs of these animals, no gross or microscopic changes due to HC Red #3 were noted. HC Red #3 was mutagenic in the Ames assay; the mutagenicity was greatly increased by metabolic activation. In a two-year feeding study, there was no evidence of carcinogenicity produced in either male or female rats. There was equivocal evidence for the carcinogenicity of HC Red #3 in male mice and inadequate evidence to make a judgement of carcinogenicity in female mice. On the basis of the available data presented in this report, it is concluded that HC Red #3, which does not contain nitrosamines and used in products not containing N-nitrosating agents, is safe as a "coal tar" hair dye ingredient at the current concentrations of use.

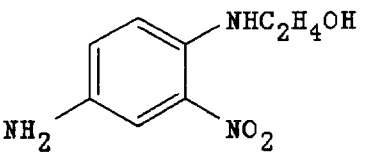
INTRODUCTION

HC RED #3, ALSO KNOWN as N1-(2-hydroxyethyl)-2-nitro-*p*-phenylenediamine, is a hair colorant used in semipermanent hair dyes. The animal toxicity and carcinogenicity data of this compound are reviewed in this report.

CHEMISTRY

Definition and Structure

HC Red #3 (CAS No. 2871-01-4) is the aromatic amine that conforms to the following formula:



Other names for HC Red #3 include N1-(2-hydroxyethyl)-2-nitro-*p*-phenylenediamine and 2-[(4-amino-2-nitrophenyl)amino]Ethanol (Estrin et al., 1982).

Chemical and Physical Properties

HC Red #3, molecular weight 197.2, occurs as fine dark red crystals with a melting range of 126.8–128°C. The UV/visible absorption maxima are 506, 298, and 245 nm. Infrared (IR) and nuclear magnetic resonance (NMR) spectra are available (NTP, 1986).

Method of Manufacture

HC Red #3 is formed by the nitration of *p*-fluoroaniline and subsequent reaction with MEA (CTFA, 1991).

Impurities

Tests on two separate batches of HC Red #3 were conducted on the reagent's identity and purity. The test material, stored at 22°C, was greater than 97% pure using water and elemental analysis, thin-layer (TLC) and high-performance liquid chromatography (HPLC), and titration of one amine group. The two major impurities (>1%) were identified. One impurity was 4'-amino-2',3-dinitro-4-(2-hydroxethylamino)-diphenylamine, an analog of HC Red #3. The other impurity was reported to be a heterocyclic fused-ring compound, either an aminoquinozaline or an aminonaphthyridine. Nitrosamines were found in both batches, at concentrations of 20 ± 5 and 11 ± 8 ppm. The identities of the nitrosamines were not investigated (NTP, 1986).

COSMETIC USE

The only reported use of HC Red #3 is in hair dyes. Data submitted to the Food and Drug Administration in 1984 by cosmetic firms participating in the voluntary cosmetic registration program indicated that HC Red #3 was used in a total of 68 hair dyes and colors. HC Red #3 was used in 16 products in a concentration range of 0.1–1%; 52 products in a range of 0–0.1% (FDA, 1984) (Table 1).

Voluntary filing of product formulation data with FDA by cosmetic manufacturers and formulators conforms to the prescribed format of preset 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

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*
Hair dyes/colors (requiring a cautionary statement)	811	68	0	16	52

Source: FDA, 1984.

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 HC Red #3 are applied to or may come in contact with hair, skin (particularly the scalp), eyes, and nails. Individuals dyeing their hair may use such formulations as often as once a week. Hairdressers may come in contact with products containing HC Red #3 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 HC Red #3, 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 eye-brows; to do so may cause blindness.

Patch test 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).

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 hours 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.

ANIMAL TOXICITY

Acute Toxicity

Doses of 62, 125, 250, 500, and 1000 mg/kg of HC Red #3 were mixed with 1% carboxymethyl-cellulose in saline and administered once, by gavage, to F344/N rats, five animals of each sex per dose group. The same method was used for $B6C3F_1$ mice; doses: 31, 62, 125, 250, and 500 mg/kg. The animals were weighed on the date of administration and observed twice daily for 15 days, and then weighed again. All of the animals survived to the end of the study, and mean body weight changes were not affected by the test material. An orange to red discoloration of the urine was observed in all dosed rats and mice for 1 day after administration (NTP, 1986).

HC Red #3, a 10% suspension in 3% acacia, was administered via gavage to Sprague-Dawley rats. Dose groups were 1250 and 5000 mg/kg for male rats and 1250, 2500, and 5000 mg/kg for female rats (5 rats/dose group). In male rats, the LD_{50} was between 1250 and 5000 mg/kg; in females; between 2500 and 5000 mg/kg (CTFA, 1991).

Short-Term Toxicity

NTP (1986) methods were applied to a 14-day study. Doses were administered daily for 14 days. On day 14, the animals were weighed and necropsied. None of the animals died during the test period. The test material did not affect mean weight gain in any dose group. All of the rats in the 1000 mg/kg dose group, and two rats each in the

[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.

500 and 250 mg/kg dose groups had pigmented thyroid glands. All dosed animals had discolored urine throughout the test period (NTP, 1986).

Subchronic Toxicity

NTP (1986) performed a 13-week study with B6C3F$_1$ mice and F344/N rats. Groups consisted of 10 animals of each sex. Mice received doses of 15, 31, 62, 125, and 250 mg/kg of HC Red #3 in corn oil; rats: 62, 125, 250, 500, and 1,000 mg/kg. Doses were administered by gavage daily. All animals were checked twice daily, the moribund animals were killed. Weights were measured and clinical examinations were performed weekly. At the end of the study, necropsy and histopathologic examination on a variety of tissues were performed. All deaths in the mice were attributed to poor gavage technique. The mean body weight of male mice in the highest dose group was reduced by 7% relative to the control, the remainder of the groups were unaffected. Except for discoloration of urine throughout the study, no other clinical signs and no microscopic or gross lesions due to the test compound were observed.

All of the rats survived to the end of the test period. In the 1,000 mg/kg male rat dose group, the mean body weight was reduced by 7% and pigmentation granules were found in the cytoplasm of epithelial cells in the thyroid gland and the kidneys. Females of this dose group had no weight depression, but had the same pigmentation of the thyroid glands and kidneys. Male rats in the 500 mg/kg group had a mean body weight 5% lower than controls; all had pigmented thyroid glands and 7 had pigmented kidneys. Females of this group showed no weight suppression; 7 had pigmented thyroid glands and all had pigmented kidneys. In the 250 mg/kg dose groups, 6 males and 7 females had pigmentation of the kidneys. All rats had orange to purple urine during the study. No other pathologic effects due to HC Red #3 were noted.

Chronic Toxicity

A two-year study of HC Red #3 was performed by NTP (1986) using the gavage method. In B6C3F$_1$ mice, groups of 50 animals of each sex were given 125 or 250 mg/kg of HC Red #3 in corn oil 5 days a week for 104 weeks. In F344/N rats, groups of 50 animals of each sex were given 250 or 500 mg/kg of HC Red #3 in corn oil 5 days a week for 105 weeks. Animals were observed twice a day, weighed and palpated weekly. At the end of the study, necropsy and histologic examination on a variety of tissues were performed.

Dosed rats of both sexes had little to no difference in survival and mean body weights as compared to controls. No adverse clinical signs attributable to HC Red #3 were noted. There were dose-related incidences of nephropathy in female rats, but the severity was inversely related to the dosage. The seminal vesicle was minimally atrophied in the dosed rats. Almost all dosed rats had pigmented kidneys, thyroid glands, or multiple organs. Retinopathy and cataracts were attributed to cage placement and not to the test compound.

In the male mice low-dose group, survival was significantly greater than the high dose group or the control. Survival of all female groups of mice was low in comparison to historical controls; this was attributed to reproductive tract infections. Mean body weights of the low, but not the high, dose groups of both sexes were slightly lower than the controls. There was suppurative inflammation of the uterus, ovary or multiple organs in female mice along with dose-related increases in organ pigmentation. Organ

cultures of moribund mice with this inflammation were positive for *Klebsiella pneumoniae*. Nephrosis was observed in female groups, but was thought to be related or secondary to this infection. Male mice had dose-related increases in organ pigmentation and cystic hyperplasia.

Ocular Irritation

HC Red #3, 100 mg in powder form, was instilled into the left eyes of 4 New Zealand White rabbits. The right eyes were untreated. Two of the rabbits had their eyes rinsed with 20 ml of distilled water 20 sec after instillation. Animals had conjunctival redness, swelling, and discharge in treated and rinsed eyes after 1 h. Similar irritation, with the addition of low-grade corneal opacity with ulceration in one eye, occurred in the treated and unrinsed eyes. After one day, treated eyes were just slightly red. All signs of irritation had disappeared after 3 days (CTFA, 1991).

Dermal Studies

Primary irritation.

HC Red #3, 500 mg as an aqueous slurry, was applied to the backs of 6 New Zealand White rabbits and left in nonoccluded contact with the skin for 24 h. Sites were scored after 24 and 72 h postapplication. There was no dermal irritation produced by HC Red #3 (CTFA, 1991).

Photosensitization.

The photosensitization potential of HC Red #3 was studied using Hartley albino guinea pigs. For 4 consecutive days during the first week of induction, 0.1 ml of 2% HC Red #3 was applied to a 1.8 cm diameter area of 8 female and 8 male shaved and depilated guinea pigs (nuchal area). After 1 h, animals were irradiated with a 150 W Xenon Lamp with a WG-354 glass filter for 7 min, which was equal to one half the minimal erythemal dose (MED) for UVA light in guinea pigs. During the second and third week of induction, HC Red #3 was applied to the same sites as before. After 1 h, animals were irradiated with the same light source without the filter for 60–120 sec, which is equal to 1 MED UVB light in guinea pigs. On days 1 and 3 of these two weeks, animals were injected with 0.1 ml of Freund's Complete Adjuvant in saline in an area surrounding the test site. The challenge phase, 2 weeks after the completion of the induction phase, consisted of the application of HC Red #3 to 3 sites in the left lumbar area. One area was irradiated with one-half the MED UVA light; another area, one-half the MED UVB light; and the third area was not irradiated. Musk ambrette, 5%, was used as a positive control (4 male and 4 female guinea pigs treated as above). There was neither irritation nor sensitization to HC Red #3 throughout the study. Seven of the 8 positive control animals had sensitization reactions (CTFA, 1991).

Reproductive Studies

A semipermanent hair-coloring composite containing 0.02% HC Red #3 was administered to groups of 10 male and 20 female rats in their diets in concentrations of 1950, and 7800 ppm. In the first study, males were fed the test diets 8 wk prior to mating and during mating, and females were fed the basal diet. In the second study, females were fed the test diet 8 wk prior to mating, during gestation, and for 21 days of lactation, and males were fed the basal diet. In both studies, no dose-related significant

differences were observed in male and female fertility, length of gestation, number of females with absorption sites, live pups per liter, pup body weights, and pup survival. There were no abnormal pups. No effects on feed consumption or body weight gains of either sex were found. In a third study, the composite was administered in the diet in the same concentrations as in the first two studies to groups of 20 pregnant rats on days 6 to 15 of gestation. The rats were sacrificed on day 19. The composite had no adverse effects on pregnant rats or pups. No dose-related significant differences were found in the average numbers of implantation sites, live pups, early or late resorptions per litter, or the number of females with one or more resorption sites. One of 244 pups was grossly abnormal in the 1950 ppm group, and 1 of 262 was grossly abnormal in the 7800 ppm composite dietary group. The litter in the high-dose group with an abnormal pup also included 13 normal pups (Wernick et al., 1975).

MUTAGENICITY

The genetic toxicity of HC Red #3 was studied in 4 different strains of *Salmonella typhimurium* in concentrations of 33, 100, 333, 1,000, and 3,333 μg/plate. Metabolic activation by liver S9 from Aroclor 1254-induced male Sprague-Dawley rats or Syrian hamster was also included. HC Red #3 was mutagenic in *S. typhimurium* strains TA97, TA98 and TA100 (but not TA1535), and this activity was greatly enhanced with both types of S9 fractions (NTP, 1986).

CARCINOGENICITY

The carcinogenicity of technical grade HC Red #3 was studied during an NTP (1986) 2-year study. In male $B6C3F_1$ mice, the occurrence of hepatocellular adenomas and carcinomas were significantly greater for the 250 mg/kg dose group than the control; the 125 mg/kg dose group, however, had fewer neoplasms than the control. The incidence of neoplasms in the high-dose group was greater than any other corn oil vehicle control in the group's studies. A trend test indicated the incidence of neoplasms to be significant in dosed mice. However, there is a variability of hepatic cell neoplasms in the males of this strain of mice and a lack of corresponding evidence for an increased incidence of hepatic neoplasms in female dose groups.

Young (1989) reviewed a number of long-term rodent studies including the NTP study of HC Red #3. When the incidence of hepatic cell neoplasms for each cage is arranged in shelf order—low dose, control, high dose—the response relates to shelf height. The occurrence of all other neoplasms in dosed groups was not significantly different than controls. Based on these data, the panel concluded that there was equivocal evidence for the carcinogenicity of HC Red #3 in male $B6C3F_1$ mice. Furthermore, NTP concluded that, due to poor survival rates, there was an inadequate study of carcinogenicity for female $B6C3F_1$ mice. The results are summarized in Table 2.

In female F344/N rats, the 250 mg/kg, but not the 500 mg/kg, dose groups had increased mammary gland neoplasms compared to the vehicle control group. The incidence of other neoplasms in rats were considered to be affected by the compound, but in a negative trend. These effects include: malignant adrenal gland pheochromocytoma in male groups, thyroid gland C-cell neoplasms in male groups, uterine endometrial stromal sarcoma in female groups, and mononuclear cell leukemia in all groups. All other neoplasms in the dosed groups were considered to be not significantly

TABLE 2. 2-YEAR STUDIES

	Vehicle control	*125 mg/kg*	*250 mg/kg*	*Historical*
Liver Neoplasms in Male Mice				
Hepatocellular Adenoma				
Overall occurrence	11/50	6/50	16/50	133/1084
Terminal rates	9/30	4/41	13/29	
Hepatocellular Carcinoma				
Overall occurrence	17/50	9/50	21/50	222/1084
Terminal rates	7/30	7/41	10/29	
Combined Adenoma and Carcinoma				
Overall occurrence	25/50	15/50	35/50	340/1084
Terminal rates	14/30	11/41	22/29	
Mammary Gland Neoplasms in Female Mice				
Fibroadenoma				
Overall occurrence	14/50	24/50	11/50	269/1084
Terminal rates	13/39	19/38	9/34	
Cystadenoma				
Overall occurrence	0/50	1/50	0/50	
Adenocarcinoma				
Overall occurrence	0/50	1/50	2/50	
Combined Cystadenoma or Fibroadenoma				
Overall occurrence	14/50	25/50	11/50	
Terminal rates	13/39	19/38	9/34	

Source: NTP, 1986.

different from controls. The NTP panel concluded that there was no evidence of carcinogenicity for HC Red #3 in both sexes of F344/N rats. An additional statement was made that the sensitivity of both mouse and rat studies may have been limited, results of toxicity studies indicated that the mice could probably have tolerated greater doses of the test material (NTP, 1986).

CLINICAL ASSESSMENT OF SAFETY

Sensitization

A repeated insult patch test on various materials, including HC Red #3, was performed on 100 volunteers. During the induction phase, 0.1 ml of an HC Red #3 gel was applied with an occlusive patch to intact skin every 48 h for a total of 10 applications. Sites were scored prior to each new application. An 11-day nontreatment period followed. The challenge phase consisted of a single 48-h patch. Sites were graded immediately and 24 h after removal of the patch. There was neither irritation nor sensitization to HC Red #3 throughout the study. Another repeated insult patch test, performed exactly as the previous study, was done on a different group of 100 volunteers. There was no irritation or sensitization to HC Red #3 throughout the study (CTFA, 1991).

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 (Anthony and Thomas, 1970; Cole et al., 1972; 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 urinary bladder cancer in men or women (Jain et al., 1977) and breast cancer in women (Shafer and Shafer, 1976; Kinlen et al., 1977; Nasca et al., 1977; Shore et al., 1979; Hennekens et al., 1979; Wynder and Goodman, 1983) 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 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 HC Red #3, 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.

The LD50 for HC Red #3 was greater than 500 mg/kg in $B6C3F_1$ mice and greater than 1000 mg/kg in F344/N rats. In a subchronic feeding study, the mean body weights of male mice and rats in the highest dose groups were reduced by 7% compared to

controls. Other than a discolorization of the urine and some organs of these animals, no gross or microscopic changes due to HC Red #3 were noted. There was not significant difference in dose and control groups in a chronic feeding study with HC Red #3, with the exception of discolorization of the urine and pigmentation of some organs.

HC Red #3 was mutagenic in three *S. typhimurium* systems. The mutagenicity was greatly increased by metabolic activation.

The carcinogenicity of HC Red #3 was studied in a two year feeding study by the NTP. In male $B6C3F_1$ mice there was an increased occurrence of liver neoplasms. However, due to the variability of neoplasms in male $B6C3F_1$ mice and the lack of corresponding evidence in female mice, NTP concluded there was equivocal evidence for the carcinogenicity of HC Red #3 in male $B6C3F_1$ mice. Because of poor survival rates, there was inadequate evidence to make a judgment of carcinogenicity in female $B6C3F_1$ mice. NTP concluded that there was no evidence for carcinogenicity in male and female F344/N rats.

DISCUSSION

The CIR Expert Panel recognizes that HC Red #3 is a mutagen and that the carcinogenicity data are difficult to interpret due to their variability. The Panel sees no reason to disagree with the final assessments of NTP that there is no conclusive evidence that this ingredient is carcinogenic in rodents. The presence of nitrosamine impurities is also of concern to the Panel. Hair dyes containing HC Red #3 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 testing 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 available data presented in this report, the CIR Expert Panel concludes that HC Red #3 is safe as a "coal tar" hair dye ingredient at the current concentrations of use, with the condition that it should not be used in products containing N-nitrosating agents.

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