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Final Report on the Safety Assessment of 4-Chlororesorcinol[1]

Abstract: 4-Chlororesorcinol is a halogenated phenol that is used as a hair colorant in over 30 hair dye and color products, generally at concentrations <1%. Hair dye and color products containing 4-Chlororesorcinol will generally have a warning statement and patch test instructions for determining if each individual user is sensitive to the product before use. The available data do not suggest that 4-Chlororesorcinol is particularly toxic. The oral median lethal dose in rats was 369 mg/kg. Subchronic dermal exposure of rats to a hair dye product containing 2% 4-Chlororesorcinol produced no evidence of compound-induced toxicity. At that same dermal exposure, no embryotoxic or teratogenic effects, no evidence of reproductive toxicity, and no carcinogenic effects were seen. Likewise, 4-Chlororesorcinol was not mutagenic in either a micronucleus or Ames test, not did it induce aneuploidy in neurospora. A 2.5% solution was not a dermal irritant or an ocular irritant in rabbits. While there was some concern that impurity data were not available, the use of actual formulations in the reproductive toxicity and carcinogenicity studies failed to produce any evidence of toxicity. On the basis of the information in the report, it was concluded that 4-Chlororesorcinol is safe as currently used in hair dye formulations. **Key Words:** 4-Chlororesorcinol—Hair colorant—Toxicity—Sensitivity—Mutagenicity.

4-Chlororesorcinol is a halogenated phenol that is used in hair dyes and colors (Wenninger and McEwen, 1992).

CHEMISTRY

Definition and Structure

4-Chlororesorcinol (CAS No. 95-88-5) is the halogenated phenol that conforms to the formula shown in Fig. 1 (Wenninger and McEwen, 1993). It is also known as 1,3-benzenediol, 4-chloro; 4-chloro-1,3-benzenediol (Wenninger and McEwen, 1993); resorcinol, 4-chloro [Lide, 1993; Registry of Toxic Effects of Chemical Substances (RTECS), 1993]; and 4-chloro-1,3-dihydroxybenzene (Lide, 1993).

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel.

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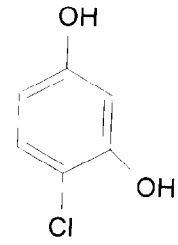

FIG. 1. Chemical formula for 4-Chlororesorcinol (Wenninger and McEwen, 1993).

Physical and Chemical Properties

The physical and chemical properties of 4-Chlororesorcinol are summarized in Table 1. Published data on the ultraviolet absorbance of 4-Chlororesorcinol were not found.

Manufacture and Production

Published data on the manufacture and production of 4-Chlororesorcinol were not found, nor were data on its impurities.

Analytical Methods

4-Chlororesorcinol has been identified in water by electron impact mass spectrometry, comparison with mass spectrum of authentic standards, and high-performance liquid chromatography retention time compared with authentic standard (Crathorne et al., 1984).

USE

Cosmetic

4-Chlororesorcinol is reported to function as a hair colorant in all types of hair dye and color products that require caution statements and patch tests (Wenninger and McEwen, 1992). The product formulation data submitted to the Food and Drug Administration (FDA) in 1994 reported that 4-Chlororesorcinol was used in 33 hair dye and color formulations (see Table 2) (FDA, 1994). Concen-

TABLE 1. *Physical and chemical properties of 4-Chlororesorcinol*

		Reference
Empirical formula	$C_6H_5ClO_2$	Wenninger and McEwen, 1993
Molecular weight	144.56	Lide, 1993
Solubility	Soluble in water, ether, alcohol, acetone, benzene	Lide, 1993
Melting point	89 or 105°C	Lide, 1993
Boiling point	259°C	Lide, 1993
K_{ow}		
In a strongly acidic water layer	62.8 ± 5	Banerjee et al., 1984
In a phosphate buffer at pH 7.0	3.91	

TABLE 2. *Cosmetic product formulation data on 4-Chlororesorcinol (FDA, 1994)*

Product category	Total no. of formulations in category	Total no. formulations containing ingredient
Hair dyes/colors (All types requiring caution statement and patch test)	1,458	33

tration of use values are no longer reported to the FDA by the cosmetic industry (Federal Register, 1992). However, the product formulation data submitted to the FDA in 1984 stated that 4-Chlororesorcinol was used in 39 hair dye and color formulations that required caution statements at a concentration of ≤1% (Table 3) (FDA, 1984).

Hair coloring formulations are applied to or may come in contact with hair, skin (particularly at the scalp), eyes, and nails. Individuals who dye their hair may use such formulations once every few weeks, whereas hairdressers may come in contact with products containing these ingredients several times a day. Under normal conditions of use, skin contact with hair dye is restricted to 30 min. The hair dyes containing 4-Chlororesorcinol, as coal tar hair dye products, 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 the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The following caution statement should be displayed conspicuously on the labels of coal tar hair dyes:

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

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

> The Cosmetic Ingredient Review (CIR) 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 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

TABLE 3. *Concentration of use of 4-Chlororesorcinol (FDA, 1984)*

	Concentration of use (%)			
Product category	0.1–1	0–0.1	Unknown	Total
Hair dyes/colors	10	25	4	39

Group (North American Contact Dermatitis Group, 1980; Eiermann et al., 1982; Adams et al., 1985). 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 48 and 72 hours 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 (Elder, 1985).

During the August 26–27, 1991 public meeting of the CIR Expert Panel, all members agreed that the cosmetic industry should change its recommendation for the evaluation of the open patch test from 24 hours to 48 hours 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 cosmetic 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.

Published data on the international use and on the noncosmetic use of 4-Chlororesorcinol were not found.

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, Excretion

Published data on the absorption, distribution, metabolism, and excretion of 4-Chlororesorcinol were not found.

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

Groups of 10 fasted CFY rats, five males and five females per group, were dosed with 4-Chlororesorcinol in aqueous solution containing 0.05% anhydrous sodium sulfite by oral intubation to determine the oral median lethal dose (LD_{50}) (Lloyd et al., 1977). A group of controls was dosed with vehicle only. Rats were observed for 14 days after dosing. The oral LD_{50} of 4-Chlororesorcinol for CFY rats was 369 mg/kg. Lethargy and piloerection were observed following dosing. Changes observed upon macroscopic examination included, in many cases, darkening of the liver and kidneys, darkening or pallor of the spleen, hemorrhage of the lungs and intestines, and congestion of the intestinal and mesenteric blood vessels. Groups of 10 CFY rats, five males and five females per group, were dosed with a total of 600 mg/kg 4-Chlororesorcinol by gastric intubation (Hossack and Richardson, 1977). The dose, which was determined in preliminary studies to be near lethal, was administered as two equal portions in 0.5% (w/v) gum tragacanth containing 0.05% (w/v) sodium sulfite given 24 h apart. A control group was dosed with vehicle only. The animals were killed 6 h after the last dose. Signs of toxicity included agitation and/or convulsions and/or lethargy. One animal died during the study.

Subchronic Toxicity

Dermal

Groups of 12 New Zealand White rabbits, six males and six females per group, were used to determine the percutaneous toxicity of an oxidative hair dye formulation containing 2% 4-Chlororesorcinol (Burnett et al., 1976). The formulation was mixed with an equal volume of 6% hydrogen peroxide, and 1 ml/kg of the mixture was applied twice weekly for 13 weeks to clipped sites on the dorsolateral aspects of the thoracic-lumbar area (one on each side of the midline), with the sites being alternated to minimize dermal irritation. The application sites on three animals per sex per group were abraded for the first dose of each week. The animals were restrained for 1 h following dosing and then washed and rinsed. Three groups of negative control animals were treated in the same manner as the test animals with the exception that no dye was applied. All animals were weighed weekly. Hematological, clinical chemistry, and urinary determinations were made at study initiation and after 3, 7, and 13 weeks. All animals were killed after 13 weeks and examined grossly. Various organ-to-body weight ratios were determined, and a number of tissues were examined microscopically. No evidence of compound-induced toxicity was observed. No discoloration of the urine due to administration of the hair dye formulation was found.

Dermal Irritation

Using the methods described in the Code of Federal Regulations (Title 16, Sec. 1500.41) for determining primary dermal irritation potential, a 2.5% (w/v) solution of 4-Chlororesorcinol was applied to the intact and abraded skin of three New Zealand White rabbits (Lloyd et al., 1977). The animals were observed for 72 h. None of the animals had an irritation response, and the primary irritation index was zero.

Ocular Irritation

Using the methods described in the Code of Federal Regulations (Title 16, Sec. 1500.42) for determining ocular irritation potential, a 2.5% (w/v) solution of 4-Chlororesorcinol was placed in the conjunctival sac of one eye of each of three New Zealand White rabbits (Lloyd et al., 1977). The eyes were rinsed 10 s after application of the test material. Transient mild conjunctival inflammation occurred, but did not persist for >24 h. 4-Chlororesorcinol was considered to be essentially nonirritating to the eyes of rabbits.

Reproductive and Developmental Toxicity

Dermal

Groups of 20 gravid Charles River CD rats were used to evaluate the teratogenic potential of an oxidative hair dye formulation containing 2% 4-Chlororesorcinol

(Burnett et al., 1976). The formulation was applied topically at a dose of 2 ml/kg to a shaved dorsoscapular area on days 1, 4, 7, 10, 13, 16, and 19 of gestation. The formulation was mixed with an equal volume of 6% hydrogen peroxide just before use. Three negative control groups of rats were shaved but not dosed, and rats of a positive control group were dosed orally by gavage with 250 mg/kg acetylsalicylic acid on days 6–16 of gestation. Feed and water were available *ad libitum*. All animals were weighed on the days of dosing and killed on day 20 of gestation. The only reported observation was a change in color of the skin and hair at the site of application. No signs of toxicity were reported. Body weight gains and mean feed consumption were similar for animals of the treated and negative control groups. A hair dye formulation containing 2% 4-Chlororesorcinol did not produce embryotoxic or teratogenic effects in Charles River CD rats.

Burnett and Goldenthal (1988) conducted a two-generation reproduction study using Sprague-Dawley rats that received topical applications of an oxidative hair dye formulation containing 2% 4-Chlororesorcinol. The formulation was mixed with an equal volume of 6% hydrogen peroxide. A twice weekly dose of 0.5 ml was applied to the shaved backs (~1 inch in diameter) of 40 rats. Successive applications were made to adjacent areas to minimize dermal irritation. When the rats were 100 days old, they were mated to produce an F_{1a} generation, which was eventually used in a carcinogenicity study. The pups were counted and weighed as a litter on days 0, 4, and 14 of lactation, with all litters culled to 10 pups on day 4. On day 21 of lactation, the pups were counted, sexed, and examined for pharmacological effects.

The F_0 generation was then reduced to 20 animals per group and remated to produce an F_{1b} generation. Twenty male and 20 female rats per group were chosen from the F_{1b} litters and mated after 100 days to produce F_{2a} and F_{2b} litters. Five male and five female F_{1b} parents were necropsied after weaning of the F_{2b} litters. Again following the same procedures, 20 male and 20 female F_2 patents per group were selected and mated to produce an F_3 generation. However, a viral infection resulted in poor reproductive performance for all groups, including controls, invalidating the results. Observations were made during the growth, mating, gestation, and lactation phases of the F_0 parents through the weaning of F_1 and F_2 litters. Comparisons of male and female fertility, gestation, and fetal viability indexes and body weights were made between rats of the treated and control groups.

Dermal irritation consisting of intermittent mild dermatitis was noted during the treatment period in each generation. No pharmacotoxicological signs were observed, and body weight gains, feed consumption, and survival were comparable for treated and control rats in each generation. Fertility, gestation, survival, and live birth indexes; mean numbers weaned; and mean weaning weights for each litter in each generation were also comparable for test and control animals. Microscopically, no treatment-related lesions were noted. The topical application of an oxidative hair dye formulation containing 2% 4-Chlororesorcinol did not have an adverse effect on reproductive performance or on the health and survival of the developing fetus and postnatal animals.

Oral

Gravid Sprague-Dawley rats were used to evaluate the teratogenic potential of 4-Chlororesorcinol (Picciano et al., 1983). Based on data from previous range-finding studies, two groups of seven dams were gavaged with 50 or 100 mg/kg, and a group of eight dams was gavaged with 200 mg/kg 4-Chlororesorcinol in 10 ml/kg propylene glycol on days 6–15 of gestation. A control group of 22 dams was dosed with 10 ml/kg of vehicle. Two positive control groups consisted of animals dosed with 100,000 IU vitamin A on day 9 of gestation and animals dosed with 350 mg/kg aspirin on days 6–15 of gestation; the number of animals used in the positive control groups was not stated. Dams were observed daily for signs of toxicity and were weighed on days 0, 6, 16, and 20 of gestation. All dams were killed on day 20 of gestation.

All dams appeared to be normal throughout the study. No maternal deaths occurred. Maternal weight gain for the group dosed with 200 mg/kg 4-Chlororesorcinol was decreased for the period days 6–16 compared with the control group. The 200 mg/kg dose was embryolethal, as indicated by a statistically significant increase in the number of resorptions compared with control values. No other significant differences were observed. The authors stated "there were no significant teratogenic effects observed" and that "4-Chlororesorcinol exhibited no teratogenic potential."

MUTAGENICITY

A micronucleus test was conducted using the bone marrow from femurs of CFY strain rats dosed by gastric intubation (described previously under Acute Toxicity) with a total of 600 mg/kg 4-Chlororesorcinol (Hossack and Richardson, 1977). No evidence of mutagenic potential was observed. The ability of 4-Chlororesorcinol to induce aneuploid products of meiosis in a neurospora cross between two multiply-marked strains was evaluated (Griffiths, 1979). The parental strains were heterozygous for four auxotrophic mutations on chromosome 1. Three tests were performed. 4-Chlororesorcinol did not cause a statistically significant change in the mean frequency rate of pseudo-wild-type strains compared with the controls. The mutagenic potential of 4-Chlororesorcinol was determined using *Salmonella typhimurium* strains TA1538 and TA98 with and without metabolic activation (Picciano et al., 1983). 4-Chlororesorcinol in dimethylsulfoxide (DMSO) was evaluated at a dose range of 20–1,000 μg/plate. Several runs were performed (number not specified). DMSO was used as the negative control and *m*-phenylenediamine and 2-nitro-*p*-phenylenediamine were used as the positive controls with and without metabolic activation, respectively. 4-Chlororesorcinol was not mutagenic in this assay.

CARCINOGENICITY

Dermal

A 21-month skin painting study was performed using groups of 100 Eppley Swiss Webster mice, 50 males and 50 females per group, to determine the carci-

nogenic potential of an oxidative hair dye formulation containing 2% 4-Chlororesorcinol (Burnett et al., 1980). The hair dye formulation was mixed with an equal volume of 6% hydrogen peroxide before use, and 0.05 ml of the test solution, containing 0.025 ml of the hair dye formulation, was applied to a 1-cm^2 area of clipped skin of the interscapular region. Two groups of negative controls were shaved, but not dosed. Observations were made daily, and body weights were measured monthly. After 7 months, 10 male and 10 female animals from each group were killed and necropsied, and liver and kidney weights were determined. Macroscopic and microscopic examinations were made for all animals found dead, killed due to moribund condition, or killed at study termination. Relative and absolute liver and kidney weights were not significantly different from control values. No compound-related neoplasms were observed. The researchers stated that an oxidative hair dye formulation containing 2% 4-Chlororesorcinol did not induce toxicological or carcinogenic effects.

Burnett and Goldenthal (1988) also conducted a study to determine the carcinogenic potential of an oxidative hair dye formulation containing 2% 4-Chlororesorcinol using the F_{1a} generation of Sprague-Dawley rats from their reproduction study that was previously summarized in this report. Groups of 120 rats, 60 males and 60 females per group, were used. The formulation was mixed with an equal volume of 6% hydrogen peroxide, and a twice-weekly dose of 0.5 ml was applied topically to a shaved area of the back, ~1 inch in diameter, for ~2 years. Successive applications were made to adjacent areas to minimize dermal irritation. The rats were observed daily for signs of toxicity and mortality. Body weights were measured weekly for the first 14 weeks and monthly thereafter; feed consumption was determined weekly. Biochemical measures were determined from blood and urine samples that were collected from five male and five female fasted rats per group at 3, 12, 18, and 24 months. Five male and five female rats per group were killed after ~12 months. No signs of toxicity were observed. Dermal irritation was minimal and comparable for animals in the treated and control groups. Discoloration of the stratum corneum and the hair shafts was observed in most treated rats, but it was considered insignificant. Body weight gains, survival, hematological values, biochemical measures, and urinalyses were similar for rats of the treated and control groups.

The incidence of mammary gland adenomas was significantly increased for the female test animals compared with those animals in control group 3; however, this value was not considered statistically different from those of the other two control groups. The incidence of pituitary adenomas significantly increased for female test animals compared with all three control groups. The authors noted that the "incidence of this tumor is known to be high and variable in untreated female Sprague-Dawley rats. The fact that no pituitary carcinomas occurred in this group suggests that the distribution of these tumors was not related to the experimental treatments." An oxidative hair dye formulation containing 2% 4-Chlororesorcinol was not considered carcinogenic.

CLINICAL ASSESSMENT OF SAFETY

Epidemiology

Between 35% and 45% of American women dye their hair, often at monthly intervals, over a period of years (CTFA, 1993). This estimate is drawn from market research data on hair dye product use, generally from females aged 15 to 60. A number of epidemiologic studies have investigated the association between cancer and occupation as a hairdresser or barber and between cancer and personal use of hair dyes. The World Health Organization's International Agency for Research on Cancer (IARC) empaneled a Working Group on the Evaluation of Carcinogenic Risks to Humans to review all available data on these issues. The Working Group met October 6–13, 1992, in Lyon, France (IARC, 1993). The charge to the IARC Working Group was to ascertain that all appropriate data had been collected and were being reviewed; to evaluate the results of the epidemiological and experimental studies and prepare accurate summaries of the data; and to make an overall evaluation of the carcinogenicity of exposure to humans. The IARC Working Group concluded that "there is *inadequate evidence* that personal use of hair colourants entails exposures that are carcinogenic." Hence: "Personal use of hair colourants *cannot be evaluated as to its carcinogenicity (Group 3).*" The IARC Working Group also concluded that "there is *limited evidence* that occupation as a hairdresser or barber entails exposures that are carcinogenic." Hence: "Occupation as a hairdresser or barber entails exposures that *are probably carcinogenic (Group 2A)*" (IARC, 1993). The CIR Expert Panel concludes that the relevance of the occupational data and conclusion to individuals using hair dyes is unclear.

SUMMARY

4-Chlororesorcinol is a halogenated phenol used as a colorant in hair dyes and colors that is soluble in water, ether, alcohol, acetone, and benzene. In 1994, data submitted to the FDA reported that 4-Chlororesorcinol was used in 33 hair dye and color formulations; in 1984, it was reported to be used at concentrations of $\leq$1.0%. Hair dyes containing 4-Chlororesorcinol, as coal tar hair dyes, 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 the label bears a caution statement and patch test instructions for determining whether the product causes irritation.

The oral LD_{50} of 4-Chlororesorcinol for CFY rats was 369 mg/kg. In a subchronic dermal toxicity study of a hair dye formulation containing 2% 4-Chlororesorcinol, the urine of rats was not discolored, and there was no evidence of compound-induced toxicity. A 2.5% 4-Chlororesorcinol solution was not a dermal irritant and was considered to be essentially nonirritating to the eyes of rabbits. The ability of a hair dye formulation containing 2% 4-Chlororesorcinol to induce teratogenic or reproductive effects upon dermal application was examined using rats. 4-Chlororesorcinol did not produce embryotoxic or teratogenic effects in a teratology study, and it did not have an adverse effect on either reproductive

performance or the health and survival of the developing fetus or postnatal animals in a multigeneration study. 4-Chlororesorcinol produced no teratogenic effects in an oral study in which rats were dosed by gavage with ≤200 mg/kg 4-Chlororesorcinol in propylene glycol. 4-Chlororesorcinol produced no evidence of mutagenic potential either in a micronucleus test or an Ames test, and it did not cause a significant change in the mean frequency of pseudo-wild-type strains in an assay evaluating its ability to induce aneuploid products of meiosis in a neurospora cross. A hair dye formulation containing 2% 4-Chlororesorcinol was not carcinogenic in two dermal carcinogenicity studies.

DISCUSSION

The CIR Expert Panel based its determination of safety of 4-Chlororesorcinol on the available dermal toxicity, teratogenicity, and carcinogenicity data cited in this review. The Expert Panel recognizes that impurity data are lacking; however, because actual formulations were used in many of the studies and the findings were negative, it was determined that impurity data were not necessary.

CONCLUSION

On the basis of the data included in this report, the CIR Expert Panel concludes that 4-Chlororesorcinol is safe as currently used in hair dye formulations.

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