BUFF

4-Chlororesorcinol

CIR EXPERT PANEL MEETING

SEPTEMBER 26-27, 2011

Cosmetic Ingredient Review
Commitment . . . Credibility
Since 1976

Memorandum

To: CIR Expert Panel Members and Liaisons

From: Christina L. Burnett

Scientific Writer/Analyst

Date: August 17, 2011

Subject: Re-review of 4-Chlororesorcinol

In 1996, the CIR Final Report on the safety assessment of 4-chlororesorcinol was published with the conclusion that this ingredient was "safe as currently used in hair dye formulations". A copy of the Final Report is included with this re-review.

Current uses of 4-chlororesorcinol can be found in Table 1. The number of uses for 4-chlororesorcinol has increased from 33 uses to 210. All uses reported in 1996 and at present are in hair dye and hair tint formulations. The current use concentration range in hair coloring products is 0.005-2%.

The European Commission's Scientific Committee on Consumer Safety (SCCS) issued an opinion on the safety of 4-chlororesorcinol in 2010 with the conclusion that this ingredient, while a moderate skin sensitizer, does not pose a health risk to the consumer at a maximum on-head concentration of 2.5%. The opinion as well as some data that was provided to the SCCS is incorporated in this re-review. The SCCS report is available online (http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_016.pdf). No other pertinent new data was discovered in a literature search for information published since 1996.

The task for the Panel at this meeting is to determine whether the conclusion on 4-chlororesorcinol is still valid. If it is not, an amendment should be initiated. If the conclusion is still valid, the Panel may reaffirm the original conclusion.

1101 17th St., NW, Suite 412 Washington, DC 20036-4702
Phone 202.331.0651 FAX 202.331.0088 http://www.cir-safety.org

4-Chlororesorcinol History

Original Report: In 1996, the Expert Panel published the safety assessment for 4-chlororesorcinol, which concluded that this ingredient was safe as used in hair dye formulations.

June 2011: the re-review of 4-chlororesorcinol was presented to the Panel.

SEARCH STRATEGY FOR 4-CHLORORESORCINOL

July 20, 2011: SCIFINDER search for CAS No. 95-88-5

- Limited search to references published since 1995; 755 references came back.
- Limited search to books, clinical trials,journals, preprints, reports, and reviews; 164 references came back.
- Limited search to "hair dye"; 7 references came back

	TOXLINE	PUBMED	EU
July 20, 2011			
4-Chlororesorcinol			Safe up to 2.5%
4-Chlrororesorcinol AND 1995-	7	10	
4-Chlororesorcinol AND 1995- AND hair dye	1	1	
95-88-5 AND 1995-	1		

Total references ordered: 8

Minutes

COSMETIC INGREDIENT REVIEW

C I R

MINUTES OF THE

FIFTY-THIRD MEETING

OF THE

EXPERT PANEL

December 12-13, 1994

LOEWS L'ENFANT PLAZA HOTEL

Washington, D.C.

Expert Panel Members

Wilma F. Bergfeld, M.D., Chairman

Donald V. Belsito, M.D.

William W. Carlton, D.V.M., Ph.D.

Curtis D. Klaassen, Ph.D.

Arnold L. Schroeter, M.D.

Ronald C. Shank, Ph.D.

Thomas J. Slaga, Ph.D.

Liaison Representatives

Consumer

Mary Ellen Fise, Esq.

Industry

Gerald N. McEwen, Jr., Ph.D.

FDA Contact Person

John Bailey, Ph.D.

CIR Staff

F. Alan Andersen, Ph.D.

Director/Scientific Coordinator

Adopted _____
(Date)

_____
Wilma F. Bergfeld, M.D.

1101 17th Street, N.W., Suite 310 WASHINGTON, DC 20036 202•331-0651

study using NTP methods will be needed; and (4) Ocular irritation data in animals (if available).

COCAMIDE DEA. The Panel voted unanimously in favor of issuing a Final Report with the following conclusion: On the basis of the animal and clinical data included in this report, the Expert Panel concludes that Cocamide DEA is safe as used in rinse-off products and safe at concentrations up to 10% in leave-on cosmetic products. Cocamide DEA should not be used as an ingredient in cosmetic products in which N-nitroso compounds are formed.

DI-*t*-BUTYLHYDROQUINONE. The Panel voted unanimously in favor of issuing a Final Report with an insufficient data conclusion. The data that are needed in order for the Panel to complete its safety assessment are listed in the discussion section of the Final Report as follows: (1) Concentration of use in cosmetics; (2) Purity/impurities data; (3) UV absorption data; if absorption occurs in the UVA or UVB range, photosensitization data are needed; and (4) Absorption, distribution, and metabolism data or 28-day dermal toxicity data; if significantly absorbed, teratogenicity data may be needed; (5) Dermal irritation and sensitization data; and (6) Two different genotoxicity studies, with one using a mammalian system; if positive, a dermal carcinogenicity assay performed according to NTP standards is needed.

4-CHLORORESORCINOL. The Panel voted unanimously in favor of issuing a Final Report on 4-Chlororesorcinol with the following 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.

HC RED NO. 1. The Panel voted unanimously in favor of issuing a Final Report with the following conclusion: On the basis of the animal and clinical data included in this report, the CIR Expert Panel concludes that HC Red No. 1 is safe as used in hair dye formulations at concentrations of ≤ 0.5%.

PYROCATECHOL. The Panel voted unanimously in favor of reissuing the Tentative Report (Addendum to the Final Report on Pyrocatechol) with the following revised conclusion: The CIR Expert Panel concludes that Pyrocatechol is unsafe for use in leave-on products and that the available data are insufficient to support the safety of Pyrocatechol as used in hair dyes. This conclusion supersedes the first conclusion that was issued by the Expert Panel in 1985. The issuance of a Final Report on this ingredient was anticipated at this meeting. However, the conclusion stated in the Tentative Report that was announced following the September 12-13, 1994 Panel Meeting was revised at the present meeting, and, thus, the Tentative Report has to be reissued.

CETRIMONIUM CHLORIDE, CETRIMONIUM BROMIDE, AND STEARTRIMONIUM CHLORIDE. The Panel voted unanimously in favor of issuing a Final Report with the following conclusion: On the basis of the animal and clinical data presented in this report, the CIR Expert Panel concludes that Cetrimonium Chloride, Cetrimonium Bromide, and Steartrimonium Chloride are safe for use in *rinse-off* products, and are safe for use at concentrations up to 0.25% in *leave-*

CIR Report History:

4-CHLORORESORCINOL

Scientific Literature Review: November 30, 1993

No unpublished data were received during the 90-day comment period that closed February 28, 1994.

Draft Report: February 28, 1994

The teams requested the following data via an informal request:

Both teams:

1. Function of 4-Chlororesorcinol in cosmetic formulations; the two editions of the dictionary list two different function of 4-Chlororesorcinol in hair dyes and colors (i.e., either as a cosmetic biocide/preservative or a hair colorant);
2. Concentration of use in cosmetic formulations;
3. Manufacturing data;
4. Impurity data;
5. UV absorption data.

The Belsito team also requested:

1. Human photosensitization data if absorbed in the UVA/UVB range;
2. Human repeat insult patch testing to determine incidence of sensitization.

If 4-Chlororesorcinol has a function in cosmetic formulations as something other than an oxidative hair dye, the Schroeter team also requested:

1. Absorption and distribution data;
2. Animal photosensitization data if absorbed in the UVA/UVB range;
3. Animal sensitization data;
4. Human irritation data.

Draft Report: May 23-24, 1994

No data were received in response to the informal data request. Frequency of use data was updated.

An IDA was issued on May 27, 1994 requesting the following data:

1. Concentration of use in cosmetic formulations;
2. Impurity data.

Tentative Report: September 12, 1994

No data were received in response to the IDA, which closed August 25, 1994.

At the meeting, the Expert Panel issued a Tentative Report with a "safe as used" conclusion.

Final Report: December 12, 1994

No data were received concerning the 90-day comment for the Tentative Report.

Report

TABLE OF CONTENTS

INTRODUCTION

The oxidative hair dye ingredient 4-chlororesorcinol has previously been reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel. In 1996, the safety assessment was published with the conclusion that this ingredient is "safe as currently used in hair dye formulations".[1]

Since the original review, the European Commission's Scientific Committee on Consumer Safety (SCCS) has received unpublished data on absorption, genotoxicity, irritation and sensitization that was summarized in their opinion on 4-chlororesorcinol.[2] This information has been summarized in this re-review. The conclusion reached by the SCCS was that 4-chlororesorcinol itself as an oxidative hair dye substance at a maximum on-head concentration of 2.5% does not pose a risk to the health of the consumer, apart from its moderate skin sensitising potential.[2]

CHEMISTRY

Definition and Structure

4-Chlororesorcinol (CAS No. 95-88-5) is a halogenated phenol. The molecular formula is $C_6H_5O_2Cl$. The structure is shown in Figure 1.

Physical and Chemical Properties

Physical and chemical properties of 4-chlororesorcinol can be found in the original safety assessment of 4-chlororesorcinol.[1]

USE

Cosmetic

Table 1 presents the historical and current product formulation data for 4-chlororesorcinol. According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), 4-chlororesorcinol was used in a total of 33 hair coloring formulations at the time of the first safety assessment.[1] An industry survey reported use concentrations of $\leq$ 1%. Currently, VCRP data indicate that 4-chlororesorcinol is used in 210 hair dye and hair tint formulations.[3] In a survey of current use concentrations conducted by the Personal Care Products Council, 4-chlororesorcinol is used at a concentration range of 0.005-2% in hair coloring products.[4]

4-Chlororesorcinol is considered a coal tar hair dye for which regulations require caution statements and instructions regarding patch tests in order to be exempt from certain adulteration and color additive provisions of the of the Federal Food, Drug, and Cosmetic Act. In order to be exempt, the following caution statement must be displayed on all coal tar hair dye products:

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

Product labels shall also bear a caution statement and patch test instructions for determining whether the product causes skin irritation. The CIR Expert Panel recommends that an open patch test be applied and evaluated by the beautician and/or consumer for sensitization 48 hours after application of the test material and prior to the use of a hair dye formulation.

The SCCS determined that 4-chlororesorcinol at a maximum on-head concentration of 2.5% does not pose a risk to the health of the consumer, apart from sensitization.[2]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Dermal/Percutaneous

In an in vitro percutaneous absorption study, [^{14}C] 4-chlororesorcinol at 2.5% in standard cream formulations with and without hydrogen peroxide and in an aqueous solution was applied to dermatomed pig skin.[2] The test substance (10 mg/cm^2) was applied to the skin samples for 30 minutes and then rinsed off. Measurements for radioactivity in the receptor fluid were throughout the 48 h exposure period. At the end of the exposure period, the distribution of the test material was assessed, including using a tape stripping technique. Sample collected during the study were analyzed by liquid scintillation counting.

Most of the test material in both the formulations with and without hydrogen peroxide was found in the rinsing solution (mean value $\pm$ SD = 259 $\pm$ 11.9 $\mu g_{eq}/cm^2$ with hydrogen peroxide, 268 $\pm$ 12.7 $\mu g_{eq}/cm^2$ without hydrogen peroxide). Most of the penetration that occurred happened during the first 4 h, with the penetration rate being 0.110 $\mu g_{eq}/cm^2/h$ with hydrogen peroxide and 0.108 $\mu g_{eq}/cm^2/h$ without hydrogen peroxide. After the 30 minute exposure, 0.062 $\mu g/cm^2$ (~0.024%) and 0.022 $\mu g/cm^2$ (~0.008%) of the formulations with and without hydrogen peroxide, respectively, had penetrated, and after 48 h, the respective amounts that had penetrated were 1.17 $\mu g/cm^2$ (~0.448%) and 1.69 $\mu g/cm^2$ (~0.651%). In the stratum corneum, 0.855% and 0.533% of the formulations with and without hydrogen peroxide, respectively, has adsorbed. The dose in the remaining epidermis/dermis was 0.855% and 0.533% with and without hydrogen peroxide, respectively. Total bioavailability within 48 h was 3.91 $\pm$ 2.20 $\mu g/cm^2$ (1.50 $\pm$ 0.84%) from the formulation with hydrogen peroxide and 5.05 $\pm$

2.97 μg/cm^2 (1.95 ± 1.14%) from the formulation without hydrogen peroxide. The total radioactivity recovery was 103% and 107% in the formulations with and without hydrogen peroxide, respectively.

In the aqueous solution, penetration occurred throughout the 48 h, which yielded a penetration rate of 2.03 μg/cm^2/h during the first 4 h and a penetration rate of 0.623 μg/cm^2/h for the period of 4-48 h. After 48 h, the penetrated amount was 35.8 μg/cm^2 (~14.2%). Small proportions of the dose were found adsorbed to the stratum corneum and absorbed to the epidermis/dermis. Total bioavailability within 48 h was 52.6 μg/cm^2 (20.8%). The SCCS found that this study did not follow its requirements and performed a worst case scenario calculation that incorporated 2 standard deviations for dermal absorption of 4-chlororesorcinol, which yielded values of 8.31 μg/cm^2 with hydrogen peroxide and 10.99 μg/cm^2 without hydrogen peroxide.

TOXICOLOGICAL STUDIES

Repeated Dose Toxicity

Oral – Non-Human

In a 91 day, groups of 10 male and 10 female HanBrl:WIST(SPF) rats received 0, 35, 70, or 210 mg/kg bodyweight/day 4-chlororesorcinol in bi-distilled water at a dose volume of 10 ml/kg bodyweight.[2] Additional groups of 5 animals of both sexes of the 0 and 210 mg/kg/day dose groups were used to assess recovery for 28 days post-treatment. OECD 408 guidelines were followed. This study was preceded by a 28-day oral range-finding study. During the study, 4 female rats of the 210 mg/kg/day dose group died. Necropsy of these animals did not reveal the cause of death. Spasm/tremor, hunched posture, abnormal gait, and salivation were observed in high dose males and females. These clinical signs were observed approximately 10-60 minutes post-dosing, after which the animals quickly recovered. Because of this rapid recovery, these finding could not be confirmed during detailed weekly assessments. There were no significant changes in food and water intake or body weight development in the treatment groups when compared to controls. There were also no significant ophthalmologic changes. In high dose males, reduced forelimb grip strength was observed as was an effect on lipid metabolism parameters. A yellow-brown discoloration and cloudy appearance in urine was observed in some high dose males that disappear after daily treatment cessation. In high dose females, a depressed red blood cell count was observed at treatment end. Effects on reticulocyte count and/or maturity index were also observed. All dose levels were observed with effects on the electrolyte parameters, which were of a minimal extent and were completely regressed during recovery. No changes were observed to absolute or relative mean organ weights nor were there any treatment-related gross lesions at any dose level. High dose males were observed to have minimal changes in liver-to-body weight and thymus-to-body weight that were associated with a minimally depressed body weight: these findings were considered incidental. No treatment-related changes to organ or tissue morphology were observed. This 91 day study of 4-chlororesocinol in rats concluded that a NOEL could not be established due to the changes to electrolyte parameters in all treatment groups. The NOAEL was determined to be 70 mg/kg bodyweight/day of 4-chlororesorcinol due to the effects observed in the high dose group rats.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

In an oral developmental study in HanBrl:WIST(SPF) rats, mated dams received 0, 50, 100, or 200 mg/kg body weight/day 98.1% 4-chlororesorcinol by gavage in ultra-pure water on days 6-20 of gestation.[2] This study was preceded by a range-finding study. In the main study, each dose group consisted of 22 rats. The dose volume was 10 ml/kg body weight. All rats were killed on day 21 of gestation and the dams and fetuses were examined in accordance to OECD 414.

All animals survived until day 21. In the 200 mg/kg dose group, clonic spasm or tremors were observed in all rats on all treatment days. In the 100 mg/kg dose group, tremor was noted in all rats during the first 6-11 treatment days. These clinical signs were considered treatment-related. Mean food consumption was similar in all groups, and no treatment-related effects on body weight gain were observed. There was a 100% pregnancy rate in the rats and the mean numbers of corpora lutea and implantation sites were similar in all groups. There was a slightly higher incidence of post-implantation loss was observed in the 50 and 100 mg/kg dose group when compared to the vehicle control, but these were considered incidental as there was no dose-relationship and the values were within the historical control range. There were no treatment-related macroscopic findings at necropsy. Mean fetal weights and fetal sex ratios were similar in all dose groups. No abnormalities were observed during external examination of the fetuses. No treatment-related visceral or skeletal effects were observed. This developmental toxicity study of 4-chlororesorcinol concluded that the maternal NOAEL was 50 mg/kg body weight/day and the fetal NOAEL was 200 mg/kg body weight /day.[2]

GENOTOXICITY

In Vitro

The genotoxicity of 4-chlororesorcinol was investigated in an Ames study using *Salmonella typhimurium* strains TA98, TA100, TA102, TA 1535, and TA 1537.[2] The study was conducted in triplicate in 2 independent experiments in accordance with OECD 471 guidelines. Both experiments used a concentration range of 98.1% 4-chlororesorcinol of 33-5000 μg/plate with and without S9 metabolic activation. Experiment 1 used the plate incorporation method while experiment 2 used the preincubation method. A reduction in the number of revertants occurred in some of the strains at the highest concentration tested, with and without metabolic activation. In experiment 1, the plates incubated with 4-chlororesorcinol had normal background growth up to the highest concentration in all strains with and without metabolic activation. In experiment 2, reduced background growth was observed at the highest concentration in all but the TA100 strain without S9

and in strains TA102 and TA1525 with S9. In strain TA100, reduced background growth was observed at 2500 and 5000 µg/plate with S9. No substantial increase in revertant colony numbers was observed in any strain at any concentration with or without metabolic activation, nor was there any tendency of concentration-related increase in revertant colonies. The study concluded that 4-chlororesorcinol is not genotoxic.

4-Chlororesorcinol was studied for gene mutations in mouse lymphoma L5178Y $TK^{+/-}$ cells.[2] After a range-finding test to measure cytotoxicity, 2 independent experiments were performed. The concentrations for experiment 1 ranged from 46.9-562.5 µg/ml, without S9 metabolic activation and from 5.9-46.9 µg/ml with S9 activation. In experiment 2, the concentrations were 47.5-380 µg/ml without S9 metabolic activation. The study was performed in accordance with OECD 476 guidelines. No relevant or reproducible increases in mutant frequency were observed in either experiment. The threshold of twice the mutant frequency of the corresponding solvent control was slightly exceeded at at46.9 µg/ml with S9 activation in experiment 1. The toxicity was severe at this concentration, however, with a relative total growth of 9.9%. The absolute value of the mutant frequency was rather low and was within the historical range of negative and solvent controls. No comparable effect was detected in parallel cultures, so this effect was not considered biologically relevant. This study concluded that 4-chlororesorcinol is not genotoxic at the *tk* locus of mouse lymphoma cells with or without metabolic activation.

The potential for 4-chlororesorcinol to induce chromosomal aberrations was studied in Chinese hamster V79 cells. The main study was preceded by a preliminary cytotoxicity test. In the main study, cells were incubated for 4 h with 4-chlororesorcinol in deionized water at concentrations of 200, 300, or 400 µg/ml without S9 metabolic activation or at concentrations of 2.5, 5, or 10 µg/ml with S9. The study was performed in accordance with OECD 473 guidelines. Statistically significant and biologically relevant increases in the number of cells carrying structural chromosomal aberrations were observed with treatment of 4-chlororesorcinol, both with and without metabolic activation. A more than 10-fold increase was observed when compared to the negative controls, ethylmethane sulfonate (without S9) and cyclophosphamide (with S9). Less than half of the aberrations observed were exchanges. There was no relevant increase in frequencies of polyploidy metaphases after treatment when compared to the frequencies of the controls. A slightly increased rate of endomitotic metaphases was observed in cells treated without S9. In this study, 4-chlororesorcinol induced structural chromosome aberration in mammalian cells in vitro, and it was concluded that 4-chlororesorcinol was a potent clastogen with and without metabolic activation.

In Vivo

The genotoxic potential of 4-chlororesorcinol was studied in a micronucleus test using NMRI mice.[2] A dose range finding experiment preceded the main study. In the main study, groups of 6 male and 6 female mice received single intraperitoneal doses of 0, 25, 50, or 100 mg/kg body weight 98.1% 4-chlororesorcinol in deionized water. At 20 and 40 minutes and 1 and 4 hours after treatment, the mice were killed and their blood was analyzed. An additional 3 males were treated with 100 mg/kg for each time interval to quantify the concentration of the test material in the blood. The samples were prepared in accordance with OECD 474 guidelines. The mean number of polychromatic erythrocytes was slightly decreased after treatment with 4-chlororesorcinol when compared to the vehicle control, which indicated that 4-chlororesorcinol was cytotoxic. The test material was quantified in the blood at 20 and 40 minutes after treatment, but not at later time points. There was no statistically significant increase in micronuclei in the treatment groups at any time interval when compared to the controls. The study concluded that 4-chlororesorcinol was not clastogenic or aneugenic in this micronucleus assay.

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

In data provided to the SCCS, the irritation potential of 4-chlororesorcinol was studied in 3 male New Zealand White albino rabbits.[2] The rabbits were exposed to 0.5 g of 98.1% pure test material that had been diluted with 60ml Milli-U water. The test material was applied to clipped skin for 4 h and semi-occluded. The application sites were observed for signs of irritation 1, 24, 48, and 72 h and 7 and 14 days after application. No corrosion of the skin was observed. Very slight, well defined or moderate to severe erythema and slight or moderate edema was observed after the 4 h treatment. The irritation was resolved in one animal after 14 days but persisted until study termination in the other 2 animals. It was concluded that 4-chlororesorcinol was irritating to the skin.

Sensitization

Dermal – Non-Human

In data provided to the SCCS, an LLNA study of 0%, 2.5%, 5%, 10%, 25% and 50% 4-chlororesorcinol in acetone: olive oil (4:1 v/v) was performed in groups of 5 female CBA mice.[2] The mice received the test material on 3 consecutive days. Additional groups of mice received 5%, 10%, or 25% α-hexylcinnamaldehyde as a positive control. Three days after the last treatment, all animals were injected with ^{3}H-methyl thymidine and the auricular lymph nodes were excised 5 h later. Radioactivity measurements were made after DNA was precipitated from the lymph nodes. The stimulation indices (SI) were calculated.

On day 3 of treatment, 4 of the 5 animals in the 50% dose group were found dead. Necropsy of these animals showed no abnormalities. No other mortalities or symptoms of systemic toxicity were observed in any of the remaining animals. Enlarged lymph nodes were observed in the 10%, 25%, and 50% groups. One animal in the vehicle control group

had an enlarged lymph node. The SI were 1.1, 1.5, 10.1, and 16.4 for the 2.5%, 5%, 10%, and 25% dose groups, respectively. The positive control yielded SI of 1.2, 2.7, and 16.8 at doses of 5%, 10%, and 25%, respectively. The estimated concentration for a SI of 3 (EC_3) value was calculated to be 5.8%. The SCCS determined from these results that 4-chlororesorcinol should be considered a moderate skin sensitizer.[2]

Ocular

In data provided to the SCCS, a single male New Zealand White albino rabbit was used to determine the ocular irritation potential of 4-chlororesorcinol.[2] Approximately 0.1 ml or 56.1 mg of the test material was instilled into one eye of the rabbit. Observations for irritation were made 1 and 24 h after treatment. Grade 4 opacity and epithelial damage affecting 100% of the corneal area was observed. Irritation of the conjunctiva included redness, chemosis, and discharge. Redness outside the eyelids and grey-white discoloration indicating necrosis of the eyelids and nictitating membrane were also observed. Due to the severity of the eye lesions, the animal was killed for ethical reasons after the 24 h observation period. It was concluded that 4-chlororesorcinol was corrosive to the eyes.

QSAR

The quantitative structure-activity relationship (QSAR) model was utilized to predict the sensitization potential of all hair dye ingredients registered in Europe (229 substances as of 2004).[5] The model predicted 4-chlororesorcinol to be a strong/moderate sensitizer. This matches the "moderate sensitizer" language in the SCCS opinion[2]

CLINICAL USE

Epidemiology

4-Chlororesorcinol is an oxidative hair dye ingredients. While the safety of individual hair dye ingredients are not addressed in epidemiology studies that seek to determine links, if any, between hair dye use and disease, such studies do provide broad information. A detailed summary of the available hair dye epidemiology data is available at http://www.cir-safety.org/findings.shtml

TABLES AND FIGURES

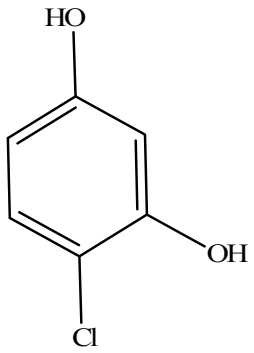

Figure 1. 4-Chlororesorcinol

Table 1. Historic and current uses and concentrations of 4-chlororesorcinol.[1,3,4]

	# of Uses		*Conc. of Use (%)*	
	4-Chlororesorcinol			
data year	*1996*	*2011*	*1996*	*2011*
Totals	**33**	**210**	**≤ 1**	**0.005-2**
Duration of Use				
Leave-On	*NA*	*NA*	*NA*	*NA*
Rinse Off	*33*	*210*	*≤ 1*	*0.005-2*
Exposure Type				
Eye Area	NA	NA	NA	NA
Possible Ingestion	NA	NA	NA	NA
Inhalation	NA	NA	NA	NA
Dermal Contact	NA	NA	NA	NA
Deodorant (underarm)	NA	NA	NA	NA
Hair - Non-Coloring	NA	NA	NA	NA
Hair-Coloring	33	210	≤ 1	0.005-2
Nail	NA	NA	NA	NA
Mucous Membrane	NA	NA	NA	NA
Bath Products	NA	NA	NA	NA
Baby Products	NA	NA	NA	NA

NA = Not Available; Totals = Rinse-off + Leave-on Product Uses.

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

References

1. Andersen FA (ed.). Final report on the safety assessment of 4-chlororesorcinol. *JACT*. 1996;15(4):284-294.

2. Scientific Committee on Consumer Safety (SCCS). Opinion on 4-Chlororesorcinol (COLIPA no. A12). European Commission Health & Consumers Directorate C: Public Health and Risk Assessment. 2010. http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_016.pdf. Report No. SCCS/1224/09.

3. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database.* 2011. Washington, DC: FDA.

4. Personal Care Products Council. 1-7-2011. Concentration of Use by FDA Product Category: 4-Chlororesorcinol. 2 pages.

5. Sosted H, Basketter A, Estrada E, Johansen JD, and Patlewicz GY. Ranking of hair dye substances according to predicted sensitization potency: Quantitative structure-activity relationships. *Contact Dermatitis*. 2004;51241-254.

Data

Journal of the American College of Toxicology
15(4):284–294, Lippincott–Raven Publishers, Philadelphia

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).

---

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

Address correspondence and reprint requests to Dr. F. A. Andersen at Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, D.C. 20036, U.S.A.

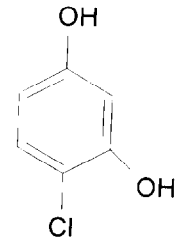

FIG. 1. Chemical formula for 4-Chlororesorcinol (Wenninger and McEwen, 1993).

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.

Acknowledgment: Monice Zondlo Fiume, Scientific Analyst/Report Management Coordinator, prepared this report.

REFERENCES

Adams RM, Maibach HI, Clendenning WE, et al. (1985) A five-year study of cosmetic reactions. *J Am Acad Dermatol* 13:1062–9.

Banerjee S, Howard PH, Rosenberg AM, Dombrowski AE, Sikka H, Tullis DL. (1984) Development of a general kinetic model for biodegradation and its application to chlorophenols and related compounds. *Environ Sci Technol* 18:416–22.

Burnett CM, Goldenthal EI. (1988) Multigeneration reproduction and carcinogenicity studies in Sprague-Dawley rats exposed topically to oxidative hair-colouring formulations containing *p*-phenylenediamine and other aromatic amines. *Food Chem Toxicol* 26:467–74.

Burnett C, Goldenthal EI, Harris SB, et al. (1976) Teratology and percutaneous toxicity studies on hair dyes. *J Toxicol Environ Health* 1:1027–40.

Burnett C, Jacobs MM, Seppala A, et al. (1980) Evaluation of the toxicity and carcinogenicity of hair dyes. *J Toxicol Environ Health* 6:247–57.

Cosmetic, Toiletry, and Fragrance Association (CTFA). (1993) Personal correspondence from G. N. McEwen. (Dated: 12/06/93).*

Crathorne B, Fielding M, Steel CP, Watts CD. (1984) Organic compounds in water: analysis using coupled-column high-performance liquid chromatography and soft-ionization mass spectrometry. *Environ Sci Technol* 18:797–802.

Eiermann HJ, Larsen W, Maibach HI, et al. (1982) Prospective study of cosmetic reactions: 1977–1980. *J Am Acad Dermatol* 6:909–17.

Elder RL, ed. (1985) Final report on the safety assessment of *p*-phenylenediamine. *J Am Coll Toxicol* 4:203–66.

*Available for review from the Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, D.C. 20036, U.S.A.

Federal Register. (January 28, 1992) Modification in voluntary filing of cosmetic product ingredient and cosmetic raw composition statements: final rule. 57:3128–30.

Food and Drug Administration (FDA). (1984) Cosmetic product formulation and frequency of use data. *FDA database*. Washington, D.C.: FDA.

FDA. (1994) Frequency of use of cosmetic ingredients. *FDA database*. Washington, D.C.: FDA.

Griffiths AJF. (1979) *Neurospora* prototroph selection system for studying aneuploid production. *Environ Health Perspect* 31:75–80.

Hossack DJN, Richardson JC. (1977) Examination of the potential mutagenicity of hair dye constituents using the micronucleus test. *Experientia* 33:377–8.

International Agency for Research on Cancer (IARC). (1993) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Vol. 57. Lyon: IARC, 43–118.

Lide DR, ed. (1993) *CRC Handbook of Chemistry and Physics*. 74th ed. Boca Raton: CRC Press, 3–451.

Lloyd GK, Liggett MP, Kynoch SR, Davies RE. (1977) Assessment of the acute toxicity and potential irritancy of hair dye constituents. *Food Cosmet Toxicol* 15:607–10.

North American Contact Dermatitis Group (NACDG). (1980) Standard screening tray: 1979 vs. 1980, summary. Evanston, Ill.: American Academy of Dermatology.

Picciano JC, Morris WE, Kwan S, Wolf BA. (1983) Evaluation of the teratogenic and mutagenic potential of oxidative dyes, 4-chlororesorcinol, *m*-phenylenediamine, and pyrogallol. *J Am Coll Toxicol* 2:325–33.

Registry of Toxic Effects of Chemical Substances (RTECS). (1993) 4-Chlororesorcinol Entry. *RTECS database*. Bethesda: National Library of Medicine.

Wenninger JA, McEwen GN Jr., eds. (1992) *Cosmetic Ingredient Handbook*. 2nd ed. Washington, D.C.: CTFA, 73.

Wenninger JA, McEwen GN, Jr., eds. (1993) *International Cosmetic Ingredient Dictionary*. 5th ed. vol. 1, Washington, D.C.: CTFA, 117.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: John Bailey, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: January 7, 2011

SUBJECT: Concentration of Use by FDA Product Category: 4-Chlororesorcinol

1101 17th Street, N.W., Suite 300 | Washington, D.C. 20036-4702 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Concentration of Use by FDA Product Category
4-Chlororesorcinol

Product Category	Concentration of Use
Hair dyes and colors (all types requiring caution statement and patch test)	0.005-2%

Information collected in 2010
Table prepared January 6, 2011

FDA 2011 VCRP Data

4-CHLORORESORCINOL	192	06A Hair Dyes and Colors
4-CHLORORESORCINOL	18	06B Hair Tints