Safety Assessment of HC Yellow No. 5 as Used in Cosmetics

Status:	Re-Review for Panel Consideration
Release Date:	November 10, 2022
Panel Meeting Date:	December 5-6, 2022

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina Burnett, Senior Scientific Analyst/ Writer, CIR.

1620 L Street, NW, Suite 1200 ◇ Washington, DC 20036-4702 ◇ ph 202.331.0651
cirinfo@cir-safety.org

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina Burnett, Senior Scientific Analyst/Writer, CIR
Date: November 10, 2022
Subject: Re-Review of the Safety Assessment of HC Yellow No. 5

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a review of the safety of HC Yellow No. 5 in 2007 with the conclusion that this ingredient is safe as a hair dye ingredient in the present practices of use and concentration described in the safety assessment (identified as *originalreport_HCYellow5_122022* in the pdf).

Because it has been at least 15 years since it was published, in accord with CIR Procedures, the Panel should consider whether the safety assessment of HC Yellow No. 5 should be re-opened. An exhaustive search of the world's literature was performed for studies dated 2003 forward. No relevant published data were found. At the time the original report was written, there were no restrictions on the use of HC Yellow No. 5 in cosmetics in Europe; however, European regulations regarding cosmetic ingredients now categorize HC Yellow No. 5 in Annex II, the list of substances prohibited in cosmetic products in Europe. This is likely due to the determination by the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) that there were inadequate data to issue a safety dossier, which was reported in the original safety assessment. A historical overview, comparison of original and new use data, and the search strategy used, are enclosed herein (*newdata_HCYellow5_122022)*.

Also included for your review is a table of current and historical use data (*usetable_HCYellow5_122022*). Since this report was first considered, the frequency of use has decreased from 37 to 5 uses; however, non-hair dye uses have been reported in the 2022 VCRP data, including 2 uses in nail polish and enamel and 1 use in body and hand skin care products. In 2003, the maximum concentration reported for use in hair coloring formulations was reported to be 1.6%. A survey performed by the Council in 2022 had no reported concentrations of use.

If, upon review of the new studies and updated use data, the Panel determines that a re-review is warranted, a Draft Amended Report will be presented at an upcoming meeting.

Re-Review - HC Yellow No. 5 - History and New Data

(Christina Burnett – December 2022 meeting)

Ingredients (1)	Citation	Conclusion	Use - New Data	Results	Use - Existing Data	Results	Notes
HC Yellow No. 5 CAS# 56932-44-6	IJT-26(SUPPL. 2)2007	safe for use in hair dye formulations	frequency of use (2022) conc of use (2022)	5 no uses reported	frequency of use (2002) conc of use (2003)	37 0.2-1.6	Two current uses of HC Yellow No. 5 are reported to be in a nail polish and enamel, and another 1 use is reported to be in a body and hand skin care product. The remaining 2 uses are in hair dyes and colors. Council survey indicated this ingredient is not in current use.

NEW DATA			
Publication	**Study Type**	**Results – Brief Overview**	**Different from Existing Data?**
COSING search 10/7/2022	Annex II, list of substances prohibited in cosmetic products in Europe	HC Yellow No. 5 (listed as entry #1285 under "N1-(2-Hydroxyethyl)-4-nitro-o-phenylenediamine (HC Yellow No 5) and its salts, when used as a substance in hair dye products")	SCCNFP opinion stating there was not enough data to support safety was in the original report, but mention of HC Yellow No. 5 on Annex II was not.

Search (from 2003 on)

PubMed

("HC Yellow 5") OR (56932-44-6[EC/RN Number]) OR (260-450-0[EC/RN Number])-62 hits; 0 relevant

ECHA

No dossier for CAS # 56932-44-6 ("2-(2-amino-4-nitroanilino)ethanol") was available.

Current and historical frequency and concentration of use according to duration and exposure for HC Yellow No. 5

	# of Uses		*Max Conc of Use (%)*	
	2022[1]	**2002[2]**	**2022[3]**	**2003[2]**
Totals*	**5**	**37**	**NR**	**0.2-1.6**
Duration of Use				
Leave-On	*3*	*NR*	*NR*	*NR*
Rinse-Off	*2*	*37*	*NR*	*0.2-1.6*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*
Exposure Type				
Eye Area	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	1[a]	NR	NR	NR
Incidental Inhalation-Powder	1[a]	NR	NR	NR
Dermal Contact	1	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR
Hair-Coloring	2	37	NR	0.2-1.6
Nail	2	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR

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

[a] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

NR – no reported use

REFERENCES

1. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. College Park, MD. 2022. (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2022; received January 11, 2022.)

2. Andersen FA (ed.). Final Report on the Safety Assessment of HC Yellow No. 5. *Int J Toxicol.* 2007;26(Suppl. 2):113-124.

3. Personal Care Products Council. 2022. Concentration of Use by FDA Product Category: HC Yellow No. 5. Unpublished data submitted by the Personal Care Products Council on July 6, 2022.

International Journal of Toxicology, 26(Suppl. 2):113–124, 2007

ISSN: 1091-5818 print / 1092-874X online
DOI: 10.1080/10915810701351244

Final Report on the Safety Assessment of HC Yellow No. 5[1]

HC Yellow No. 5 is a direct hair dye. Hair dyes containing HC Yellow No. 5, as "coal tar" hair dye products, are exempt from the principal adulteration provision and from the color additive provision 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. Preliminary testing on or by individuals should be done using an open patch test that is evaluated at 48 h after application of the test material. Users, therefore, would be able to determine their individual reactions to hair dye products containing HC Yellow No. 5. Absorption of HC Yellow No. 5 is minimal through skin (<0.2%). The oral LD_{50} for rats is 555.56 mg/kg. No significant toxic effects were observed after chronic oral exposure of HD Yellow No. 5 to dogs. Mild dermal irritation, but no dermal sensitization or ocular irritation was observed in laboratory animals. Results of fertility and reproductive performance, teratology, and developmental studies were negative. HC Yellow No. 5 was found to be nonmutagenic and noncytotoxic in standard laboratory assays. A current review of the hair dye epidemiology literature identified that use of direct hair dyes, although not the focus in all investigations, appears to have little evidence of an association with cancer or other adverse events. Based on the available safety test data on HC Yellow No. 5, the Panel determined that this ingredient likely would not have carcinogenic potential as used in hair dyes. The Cosmetic Ingredient Review (CIR) Expert Panel concluded that HC Yellow No. 5 is safe as a hair dye ingredient in the practices of use and concentration as described in this safety assessment.

INTRODUCTION

This review presents information relevant to the safety of HC Yellow No. 5 as a direct hair dye cosmetic ingredient as considered by the Cosmetic Ingredient Review (CIR) Expert Panel.

CHEMISTRY

Definition and Structure

As described in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), HC Yellow No. 5 (CAS no. 56932-44-6) is the hair dye that conforms to the structure shown in Figure 1. Its empirical formula is $C_8H_{11}N_3O_3$ (Keystone Aniline Corp. 2002).

Synonyms include (Gottschalck and McEwen 2004):

- 2-[(2-Amino-4-Nitrophenyl)Amino]Ethanol,
- Ethanol, 2-(2-amino-4-nitroanilino)-,
- Ethanol, 2-[(2-Amino-4-Nitrophenyl)Amino]-, and
- N1-(2-Hydroxyethyl)-4-Nitro-*o*-Phenylenediamine.

Trade names include Jarocol Yellow 5 and Covariane Jaune W 1125, and a trade name mixture that includes HC Yellow No. 5 is Rodol 2G Y5 (Gottschalck and McEwen 2004).

ChemIDplus (2002) lists the following synonyms:

- 2-(2-amino-4-nitroanilino)-ethanol,
- N1-(2-hydroxyethyl)-4-nitro-*ortho*-phenylenediamine,
- N^1-(2-hydroxyethyl)-4-nitro-*o*-phenylenediamine,
- N^1-(2-hydroxyethyl)-4-nitro-*ortho*-phenylenediamine,
- N′-(2-hydroxyethyl)-4-nitro-*o*-phenylenediamine,
- N′-(2-hydroxyethyl)-4-nitro-*ortho*-phenylenediamine,
- N′-2-hydroxyethyl-4-nitro-*o*-phenylenediamine,
- N′-2-hydroxyethyl-4-nitro-*ortho*-phenylenediamine, and
- 2-[(2-amino-4-nitrophenyl)amine]ethanol.

Physical and Chemical Properties

According to Keystone Aniline Corp. (2002), HC Yellow No. 5 is a yellow to orange crystal or powder, with a molecular weight of 197.19 daltons, that is slightly soluble in water and alcohol at 25°C and 60°C, and has a melting point of 132°C.

Method of Manufacture

No information was found on the method of manufacturing for HC Yellow No. 5.

Analytical Methods

HC Yellow No. 5 may be determined using thin-layer chromatography, mass spectroscopy, and infrared (IR) spectroscopy (Österreichisches Forschungszentrum Seibersdorf GmbH 1997; Keystone Aniline Corp. 2002).

Impurities

The purity of HC Yellow No. 5 was reported as 98% minimum, with a maximum of 0.2% of ash and a maximum of 100 ppm of iron (Keystone Aniline Corp. 2002).

Received 30 November 2006; accepted 5 March 2007.
[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. Address correspondence to F. Alan Andersen, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036, USA.

FIGURE 1
Structure for HC Yellow No. 5 as given in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004).

USE

Cosmetic

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), HC Yellow No. 5 functions as a hair colorant. Industry reports to the Food and Drug Administration (FDA) indicate that HC Yellow No. 5 is used in 37 products in the categories of hair dye and color and hair tints as shown in Table 1 (FDA 2002). Earlier reports to FDA in 1984 indicated 5 reported uses of HC Yellow No.5 in hair dyes and colors in the concentration range of 0% to 0.1% and no uses in hair tints (FDA 1984). Current concentration of use information indicates that HC Yellow No. 5 is used at 1.6% in hair dyes and 0.2% in hair tints (CTFA 2003).

According to several sources (Corbett 1984; Keystone Aniline Corp. 2002; James Robinson Ltd. 2002), HC Yellow No. 5 is used in semipermanent dyes. Such dyes are nonoxidative. HC Yellow No. 5 may also be used as a toner in permanent, oxidative hair dyes (CTFA 2003).

Hair coloring formulations are applied to or may come in contact with hair, skin, and nails. Individuals dyeing 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.

Hair dyes containing HC Yellow No. 5, 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 "patch test" instructions for determining whether the product causes skin irritation (FDA 1979). In order to be exempt, the following caution statement must be displayed on all coal tar hair dye products:

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

At its February 11, 1992, meeting, the Cosmetic Ingredient Review (CIR) 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 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 (North American Contact Dermatitis Group 1980; Eiermann et al. 1982; Adams et al. 1985). 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 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 cosmetics 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 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.

Accordingly, preliminary testing on or by individuals should be done using an open patch test that is evaluated at 48 hours after application of the test material.

TABLE 1
Available use data for HC Yellow No. 5

Product category (number of formulations reported to FDA 2002)	Number of formulations containing HC Yellow No. 5 (FDA, 2002)	Concentration of use (%) (CTFA, 2003)
Hair dyes and colors (1690)	32	1.6
Hair tints (49)	5	0.2
Total	37	0.2–1.6

According to the Ministry of Health, Labor and Welfare (MHLW), the hair dye HC Yellow No. 5 is not prohibited in cosmetic products that are marketed in Japan (MHLW 2001).

The Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers (SCCNFP), which advises the European Commission on safety of cosmetic ingredients, included HC Yellow No. 5 on its list of substances that cannot be considered safe for hair dyeing purposes, unless they are regarded as such on the basis of an adequate safety dossier (European Commission 2004).

Noncosmetic

No information was found on noncosmetic uses for HC Yellow No. 5.

BIOLOGICAL PROPERTIES

Absorption, Distribution, Metabolism, and Excretion

Österreichisches Forschungszentrum Seibersdorf GmbH (1997) conducted a series of tests to determine the percutaneous penetration of HC Yellow No. 5, the distribution of label in various organs, and the mode and rate of elimination in rats.

HC Yellow No. 5 (1.875% unlabeled and 1.125% ^{14}C-labeled) in aqueous solution, which appeared to mimic a hair dye product, was applied using a spatula to a 3-cm^2 area of the clipped dorsal skin on Sprague-Dawley rats. Animals were restrained during the 30-min application period, after which time the test material was removed with a spatula followed by shampooing and thorough rinsing. The exposed skin was covered with gauze that was attached using tape and animals were placed in metabolism cages.

Six animals received 0.2 g of the HC Yellow No. 5 solution (mean HC Yellow No. 5 dose of 31.4 mg/kg) and another six animals received 0.1 g of the solution plus 0.1 g of hydrogen peroxide developer (mean HC Yellow No. 5 dose of 15.1 mg/kg).

Animals were held in the metabolism cages for 72 h and then killed. Urine and feces were collected over each of three 24-h periods. The hair at the site of application was removed by shaving and analyzed for radioactivity. The stratum corneum at the site of application was obtained by six tape strippings. The remaining epidermis and dermis at the application site were excised. The adrenal glands, blood, brain, fat, femur, heart, kidneys, liver, lung, muscle, ovaries, untreated skin, spleen, and thyroid glands were also removed and analyzed for radioactivity. The rest of the carcass (except for the skin) was analyzed for radioactivity.

Table 2 gives the disposition of the radioactive label in the animals exposed to the hair dye only and that of the animals exposed to the hair dye and the developer. The total recovery of radioactive label was high in both groups, and was primarily in the post-treatment rinse water. The next highest quantity was found in the hair stubs. The authors determined that the overall skin penetration was 0.054% with the hair dye alone and 0.124% with the hair dye plus developer. If the radioactivity in the dermis is presumed to penetrate eventually, these percentages increase to 0.079% and 0.198%, respectively.

For most organs and the carcass, the radioactivity was below the detectable level (indistinguishable from background levels).

TABLE 2
Percentage distribution of radioactive label in rats exposed to HC Yellow No. 5
(Österreichisches Forschungszentrum Seibersdorf GmbH 1997)

	Hair dye alone		Hair dye plus developer	
Parameter	Mean	SD	Mean	SD
Rinse water	95.6	2.3	94.3	0.83
Hair stubs	1.45	0.63	2.70	0.54
Stratum corneum	0.048	0.023	0.098	0.016
Epidermis/dermis	0.0248	0.0073	0.075	0.035
Percutaneous penetration	0.054	0.013	0.124	0.046
Urine as a function of time 0–24 hours	0.028	0.010	0.067	0.045
24–48 hours	0.00682	0.00096	0.0126	0.0049
48–72 hours	0.00277	0.00071	0.0047	0.0022
Total excreted in urine	0.037	0.011	0.084	0.045
Feces as a function of time 0–24 hours	0.0081	0.0041	0.0171	0.0089
24–48 hours	0.0051	0.0022	0.0151	0.0070
48–72 hours	0.0025	0.0011	0.0042	0.0011
Total excreted in feces	0.0157	0.0029	0.0364	0.0098
Organs/carcass	0.0011	0.00023	0.0029	0.0014
Total recovery	97.2	2.2	97.3	0.81

The only detectable levels were in the kidneys for the hair dye alone group and the kidneys and liver for the hair dye plus developer group.

Excretion of the very small absorbed amount was approximately 70% urine and 30% feces in both groups. Most of the urinary excretion (75% to 80%) occurred in the first 24 h (Österreichisches Forschungszentrum Seibersdorf GmbH 1997).

ANIMAL TOXICOLOGY

Acute Oral Toxicity

IBR Forschungs GmbH (1985a) performed an acute oral toxicity study on HC Yellow No.5 (10% suspension in water) using WISW strain rats. Two male rats (157.9 to 184.1 g) and two female rats (147.7 to 168.3 g) were used in each dose group. At 250 mg/kg, none of the animals died. At 500 mg/kg, neither of the males died, but one female died. At 625 mg/kg, one male died and both females died. At 750 mg/kg, all rats died. The LD_{50} for both sexes was calculated to be 555.56 mg/kg, but LD_{50} for females appeared lower than that of males.

Chronic Oral Toxicity

Wernick et al. (1975) performed a chronic toxicity test on 18 male and 18 female purebred Beagle dogs. The animals, 6 to 8 months of age, were divided into three groups of six males and six females. A composite material representative of commercially available semipermanent hair-coloring products was prepared by employing the highest concentration of each dye and each base component. The dyes were obtained from commercial sources and were used without further purification. Content of the composite, including HC Yellow No.5, is given in Table 3. Dosages of the composite were 0.0, 19.5, and 97.5 mg/kg/day given in the food. Each animal was observed daily for signs of toxic or pharmacologic effects. Necropsy was performed on one male and one female from each group at 6, 12, and 18 months and on all survivors at 24 months. No significant effects were observed. Urine was blue black and returned to normal color after overnight fasting. The only change in urine was the blue/black color.

Dermal Irritation

IBR Forschungs GmbH (1985b) assessed the dermal irritation of HC Yellow No. 5 (1% in water, pH 6.0) using six albino rabbits. The test material (0.5 ml) was applied to a 2.5-cm^2 patch on an area of shaved skin and on an area of shaved/abraded skin. At 24 and 72 h after application, sites were read for erythema and edema. One rabbit had erythema on both sites at 24 h, but it disappeared by 72 h. Another rabbit had erythema at 24 h only at the shaved site and this disappeared at 72 h. Erythema and edema reactions were recorded on a scale of 1 to 4 in each animal. The average irritation index for all animals at the shaved site (0.08) was combined with the average irritation index at the shaved/abraded site (0.04) to give a total primary irritation index, which the authors stated as 0.12.

Dermal Sensitization

IBR Forschungs GmbH (1985c) reported the results of a Magnusson/Kligman maximization test using guinea pigs. Twenty animals were in the treatment group, 10 in the positive-control group, and 10 in the negative-control group. Each group was comprised of equal numbers of male and female animals. HC Yellow No. 5 (1% in water) was the test material. The positive control was 1-chloro-2,4-dinitrobenzol (DNCB) and the negative control was water. Animals were injected with Freund's complete adjuvant (FCA) diluted 1:1 in water, followed by injection of HC Yellow No. 5 at 1% or DNCB at 0.005%. Negative controls received only the FCA injection. All injections were 0.05 ml. The next morning, animals were treated with sodium lauryl sulfate (10% in petrolatum) with abrasion. Six to 8 h later, the animals received the test (1%), positive-control (0.025%), and negative-control (1%) materials dermally in petrolatum (0.5 ml). The next day (48 h after the first intradermal injection) the animals received the final intradermal injection (0.05 ml) of the test or control substances in Freund's complete adjuvant, at the same concentrations as the initial injections.

Challenge exposures were done 14 days after induction. Each of three sites was exposed to decreasing concentrations of the test material (1%, 0.5%, and 0.25%) and DNCB (0.1%, 0.05%, and 0.025%) in water, or water alone in Hill Top chambers. At 24 h, the chambers were removed and the animals observed. Animals were also observed at 48 h. No irritation reactions were reported to HC Yellow No. 5 in the exposed or negative-control groups at 24 or 48 h. The positive control at 0.1% produced sensitization reactions in 10/10 animals at 24 and 48 h; 0.05% produced sensitization reactions in 8/10 animals at 24 and 48 h; and 0.025% produced sensitization reactions in 4/10 animals at 24 and 48 h (IBR Forschungs GmbH 1985c).

Ocular Irritation

IBR Forschung GmbH (1985d) assessed the ocular irritation of HC Yellow No. 5 using nine albino rabbits. Each animal received 0.1 ml of the 1% HC Yellow No. 5 (in water, pH 6.0) in the conjunctival sac of the left eye. The right eye served as the control. In three animals, the test material was allowed to stay in the eye for 4 s before rinsing. In three animals, the test material was allowed to stay in the eye for 30 s before rinsing. In three animals, the eye was not rinsed. Animals were observed for 7 days after treatment. No adverse effects of HC Yellow No. 5 were reported in any of the animals (cornea, iris, or conjunctiva) over the observation period.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Wernick et al. (1975) performed a fertility and reproductive performance study using Sprague-Dawley CD rats. Sixty males

TABLE 3
Dye/base composite (Wernick et al. 1975)

CTFA dictionary name	Chemical abstract name/dye type	%
	Dye	
Acid Orange 3	Sodium 4-anilino-2′,4′-dinitrodiphenylamine-3-sulfonate	0.24
HC Blue No. 2	2,2′-[4-[(2-Hydroxyethylamino)-3-nitrophenyl]imino]diethanol	1.63
Celliton Fast Navy Blue BRA[a]	—	0.64
2-Nitro-*p*-phenylenediamine	1,4-Diamino-nitrobenzene	0.24
4-Nitro-*o*-phenylenediamine	1,2-Diamino-4-nitrobenzene	0.16
2-Amino-4-nitrophenol	2-Amino-4-nitrophenol	0.05
HC Yellow No. 5	2-[2-Amino-4-nitroanilino]ethanol	0.05
HC Yellow No. 4	2,2′[(2-Hydroxy-4-nitrophenyl)-imino]-diethanol	0.31
Disperse Violet 11	-Anthraquinone	0.40
Disperse Blue 1		0.61
Disperse Black 9	-Diazo	0.13
HC Blue No. 1	2,2′-[[4-(Methylamino)-3-nitrophenyl]-imino]diethanol	1.54
HC Red No. 3	2-[4-Amino-2-nitroanilino]-ethanol	0.02
HC Yellow No. 3	2-bis(Hydroxymethyl)-2-[2-amino-4-nitroanilino]ethanol	0.65
HC Yellow No. 2	2-[2-Nitroanilino]-ethanol	0.28
	Base	
Lauramide DEA		20.22
Imino-bis propylamine		9.64
Cellulose ether		17.94
Citric acid		16.02
BHT		1.61
Sodium *m*-nitrobenzene sulfonate		2.25
TEA-Dodecylbenzene sulfonate		1.61
Monoethanolamine		22.42
Perfume		0.67
Perfume		0.67

[a] A mixture of: Disperse Yellow 1—2,4-Dinitro-4′-hydroxy diphenylamine; Disperse Blue 1—1,4,5,8-Tetraamino anthraquinone; Disperse Violet 4—1-Amino-4-methylamino anthraquinone; and Disperse Red 17—4-(bis-hydroxyethyl)amino-2-methyl-4′-nitrobenzene.

and 120 females were divided into six groups of 10 males and 20 females each. The composite mixture (see Table 4) was added to the feed at concentrations of 0, 1950, and 7800 ppm. Diets were prepared twice weekly. The study was divided into two parts. In Part I, the females received the basal diet from 8 weeks prior to mating through weaning. The males used to breed the females were fed the test diets for 8 weeks prior to mating and during the mating period. In Part II, males received the basal diet for 8 weeks prior to and during mating, whereas the females received the test diets 8 weeks prior to mating, during gestation, and 21 days of lactation. There were no dose-related significant differences in any parameters examined which included male and female fertility, length of gestation, number of females with resorption sites, live pups per litter, pup body weights, and pup survival.

These authors also performed a teratology study in which sixty male and sixty female virgin CFE-S 15-week-old rats were treated with the composite of dyes listed in Table 4 given in feed. The rats were divided into three groups of 20. The composite was placed in the feed at days 6 to 15 of gestation at concentrations of 0, 1950, or 7800 ppm. No gross abnormalities (not specified in publication) were noted in the low-dose group. Gross abnormality was observed in 1 of the 13 pups in the high-dose group. In the litter with the abnormal pup, there were 12 other pups that were normal. The rats in the teratology and reproductive studies excreted blue-brown urine.

TABLE 4
HC Yellow No. 5 genotoxicity studies

Test system	HC Yellow No. 5 concentration or dose	Number of animals	Results	Reference
S. typhimurium TA1535, TA1537, TA98, TA100	8, 40, 200, 1000, 5000 μg/plate	—	Concentration-dependent increase in number of revertants per plate, with or without metabolic activation; frameshift mutations speculated	Hans Schwartzkopf GmbH 1985a
Mouse micronucleus test	240 mg/kg	3 groups of 5 males and 5 females	No statistically significant effect	Hans Schwartzkopf GmbH 1985b
Mouse micronucleus test	150 mg/kg	3 groups of 5 males and 5 females	No cytotoxic or mutagenic effects noted	Österreichisches Forschungszentrum Seibersdorf GmbH 1988
Mutation assay in mouse lymphoma cells	0.46, 1.37, 4.11, 12.3, 37.0, 111.1, 333.3, and 1000 μg/ml	—	No statistically significant increase in resistant cells, with or without metabolic activation	Labor L+S GmbH 1989
Chromosome aberration in human peripheral blood lymphocytes	30, 100, and 300 μg/ml	—	No significant increase in number of aberrations with or without metabolic activation; highest concentration 50% cytotoxic	King and Harnasch GmbH 1990
Genotoxicity assay in Chinese hamster cells	78.1, 156, 313, 625, 1250, 1500, 1750, 2000, 2250 μg/ml	—	No significant increase in mutants, with or without metabolic activation; however, concentrations above 1500 μg/ml were cytotoxic in concentration-dependent manner	Research Toxicology Centre S.p.A. 1996

These authors performed another teratology study using 48 sexually mature female New Zealand white rabbits. The rabbits were artificially inseminated and placed into four groups of 12 rabbits. The rabbits received, by oral gavage, the composite mixture in Table 4 on days 6 to 18 of gestation. The doses were 19.5 or 97.5 mg/kg/day; control was 0.5% aqueous methylcellulose. The dose volume for all groups was 1 ml/kg. There was no significant evidence of teratologic effect in any dose group for the composite. Fetal survival was not adversely affected by the dye/base composite. No gross abnormalities or soft tissue defects were observed. There were variations in the degree of ossification and in the number of ribs in this species; the distribution of these changes showed no relationship to treatment. Animals receiving the high dose excreted blue-brown urine (Wernick et al. 1975) .

A study by DiNardo et al. (1985) examined the teratology of HC Yellow No. 5 using Sprague-Dawley rats. Ten to 13 pregnant rats received, by oral gavage, the dye on gestation days 6 through 15. The dye was dissolved in propylene glycol for doses of 50, 100, and 200 mg/kg. The administration volume was 10 ml/kg. There were no teratogenic effects. The high dose caused significant decrease in the mean maternal weight gains during days 6 through 16 of gestation. There was a significant increase in mean maternal weight gain for the high-dose groups during post-treatment-period days 16 to 20.

Österreichisches Forschungszentrum Seibersdorf GmbH (1999) conducted a reproductive toxicity study of HC Yellow No. 5 in Wistar rats. HC Yellow No. 5 in 0.5% aqueous sodium carboxymethylcellulose was administered by gavage once daily on days 6 to 16 of gestation at three dose levels: 40, 80, and 100 mg/kg. A vehicle-control group was also included. Each group had 30 animals.

Animals were observed daily for signs of toxicity, weighed regularly, and food consumption was determined for days 0 to 6, 6 to 11, 11 to 16, and 16 to 20 of gestation. Animals were necropsied on day 20 of gestation.

There were no deaths or any abnormal behavior noted during the study. Red stains on bedding and fur were noted. During the exposure period, body weight gain was reduced at all dose levels compared to controls. In the 80 and 100 mg/kg groups, food consumption was also reduced. The authors interpreted these findings as signs of maternal toxicity.

The body weights of the fetuses at all dose levels were reduced compared to the controls, but there was no apparent dose response. Only one nonskeletal malformation, anasarca, accompanied with an anemic placenta, was noted in one fetus of the 80 mg/kg test group. At all dose levels, the number of fetuses affected was not significantly greater than the controls even though there were more litters with skeletal abnormalities compared to the control group. A statistically significant increase, compared to controls, was found, when calculated per fetus for all skeletal variations and when excluding the frequently seen not/incompletely ossified sternebrae 5 and/or 6 in the 80 and 100 mg/kg groups, and for all skeletal retardations in the 80 mg/kg group.

A statistically significant increase, compared to controls, was found in the number of retardations, including

- incompletely ossified metatarsals in all dose groups;
- incompletely ossified cervical arches in the 80 and 100 mg/kg dose groups;
- partially ossified caudal vertebrae in the 40 and 80 mg/kg groups;
- incompletely ossified metacarpals in the 40 and 80 mg/kg groups;
- incompletely ossified pelvis in the 80 mg/kg group;
- poorly ossified skull in the 80 mg/kg group; and
- less than four completely ossified sternebrae in the 80 mg/kg group.

At all dose levels, there were significantly more fetuses with slightly enlarged brain ventricles (classified as a retardation) compared to the control group, but this effect was not dose related.

Other statistically significant increases, compared to controls, were found when calculated per fetus for

- all visceral retardations in all dose groups; and
- marked dilatation of the heart ventricles (classified as retardation) in all dose groups.

The authors noted several aspects of this study that argued against a causal relationship between exposure to HC Yellow No. 5 and the developmental abnormalities seen. They stated that the lower fetal body weights and the various retardations in development are due to maternal toxicity. The types of malformations seen in this study, they stated, are also seen in other studies in which maternal toxicity was seen, are common in control groups, and are not dose dependent. Therefore, they concluded that these data do not suggest that HC Yellow No. 5 is teratogenic (Österreichisches Forschungszentrum Seibersdorf GmbH 1999).

GENOTOXICITY

Table 4 presents a summary of HC Yellow No. 5 genotoxicity studies.

Bacterial Cell Assay

Hans Schwarzkopf GmbH (1985a) conducted bacterial mutagenicity tests on HC Yellow No. 5. *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 were used in a plate incorporation test, with and without metabolic activation with Aroclor-induced rat liver microsomal fraction S9. HC Yellow No. 5 dissolved in dimethylsulfoxide (DMSO) was used at five concentrations (8, 40, 200, 1000, and 5000 μg/plate). Exposures were done in triplicate and repeated in a second experiment.

Positive controls were strain and S9 induction specific. Without S9, sodium azide (SA) was used with TA1535 and TA100, 9-aminoacridine (9AA) with TA1537, and 2-nitrofluorene (2NF)

with TA98. With S9 activation, 2-aminoanthracene (2AA) was used with all strains.

At 5000 μg/plate, HC Yellow No. 5 was sufficiently toxic to reduce the background lawn of bacterial growth. No increase in the mean number of revertants per plate was seen in strain TA1535, at any concentration, with or without metabolic activation. A concentration-dependent increase in revertants per plate was seen with strains TA1537, TA98, and TA100, with or without metabolic activation. The authors speculated that HC Yellow No. 5 mutagenesis was the result of a frameshift mechanism (Hans Schwartzkopf GmbH 1985a).

Mammalian Cell Assays

Labor L+S GmbH (1989) performed a mutation assay in mouse lymphoma L5178Y cells using HC Yellow No. 5 at final concentrations of 0.46, 1.37, 4.11, 12.3, 37.0, 111.1, 333.3, and 1000 μg/ml, with and without metabolic activation by rat liver microsomal S9 fraction. Positive controls received 4-nitroquinoline-*N*-oxide at 0.19 μg/ml without metabolic activation, or benzo(a)pyrene at 2.0 μg/ml with metabolic activation.

Cell survival was reduced in a concentration-dependent manner, with and without metabolic activation, and positive controls had the expected increases in 6-thioguanine–resistant cells. There were no statistically significant increases in resistant cells in the cultures exposed to HC Yellow No. 5 at any concentration, with or without metabolic activation (Labor L+S GmbH 1989).

King & Harnasch GmbH (1990) conducted a study in which human peripheral blood lymphocytes were exposed to HC Yellow No. 5 in vitro and the induction of chromosome aberrations was determined. HC Yellow No. 5 was dissolved in DMSO and added to cell cultures to a final concentration of 30, 100, and 300 μg/ml, with and without metabolic activation by Aroclor-induced rat liver homogenate S9 fraction. Positive controls were cyclophosphamide with metabolic activation and mitomycin C without metabolic activation. Negative controls were exposed to DMSO (the final concentration of DMSO in culture was ≤0.82%).

After 48 h in complete medium, cell cultures were exposed to the test material for 24 h in studies without metabolic activation. For metabolic activation, cultures were centrifuged and cells resuspended in 4.5 ml of treatment medium to which was added 0.5 ml S9. After 2 h at 37°C, the cells were again centrifuged, washed, and resuspended in complete medium. Incubation continued to 24 h.

Positive-control exposures produced the expected increase in chromosome aberrations (gaps, chromosome deletions/exchanges, chromatid deletions/exchanges, isolocus deletions). Although treatment with the highest concentration of HC Yellow No. 5 resulted in 50% cytotoxicity, at no concentration did HC Yellow No. 5 produce a significant increase in the number of chromosome aberrations compared to the control or to historical control values in cells from the same donor (King & Harnasch GmbH 1990).

The Research Toxicology Centre S.p.A. (1996) conducted a genotoxicity test of HC Yellow No. 5 in Chinese hamster V79 cells in vitro, with and without metabolic activation by Aroclor-induced rat liver microsome S9 fraction. Exposures in the first trial using HC Yellow No. 5 (dissolved in DMSO) were at concentrations of 78.1, 156, 313, 625, 1250, 1500, 2000, and 2250 μg/ml, and in the second trial at 78.1, 156, 313, 625, 1250, 1500, 1750, and 2000 μg/ml. DMSO at 1% was used as a solvent control. The positive control was ethylmethanesulfonate.

Cell survival was reduced to 1% at 2250 μg/ml, 13% at 2000 μg/ml, 67% at 1500 μg/ml, etc., in a concentration-dependent manner in the first trial, in the absence of metabolic activation. With metabolic activation, survival was 1% at the two highest concentrations and 47% at 1500 μg/ml. Similar results were seen in the second trial. Because of the low survival (<5%) at certain concentrations, data from these concentrations were not considered in the analysis of mutations.

In the absence of metabolic activation, ≥5-fold increases in 6-thioguanine-resistant mutants were observed at the 78.1 and 625 μg/ml concentrations in the first trial. No increases were seen at the other concentrations without metabolic activation, nor at any concentration with metabolic activation in the first trial. No increases were seen, at any concentration, with or without metabolic activation, in the second trial. The authors concluded that HC Yellow No. 5 was not mutagenic in this assay (Research Toxicology Centre S.p.A. 1996).

Animal Assays

Hans Schwartzkopf GmbH (1985b) conducted a mouse micronucleus test on HC Yellow No. 5. In a range-finding study, it was determined that the maximum tolerated dose of HC Yellow No. 5 injected intraperitoneally in CFLP mice was 240 mg/kg. All animals dosed at 300 mg/kg died.

Three groups of five male and five female mice were given single intraperitoneal injections of HC Yellow No. 5 in 10% DMSO in deionized water to reach a dose of 240 mg/kg. Animals in one group were killed at 24, 48, and 72 h; bone marrow was harvested from both femurs and prepared on slides. Thirty animals received only the vehicle using the same procedure. A positive-control group of 10 animals received cyclophosphamide at 40 mg/kg and was killed at 24 h. Polychromatic erythrocytes (1000 where possible) were counted for each animal.

Although many animals (mostly males) yielded poorly distributed micronuclei or were simply uncountable, statistical analyses using the Fischer Exact test and the chi-squared test demonstrated a significant effect with cyclophosphamide, but not with HC Yellow No. 5, compared to the vehicle control (Hans Schwartzkopf GmbH 1985b).

Österreichisches Forschungszentrum Seibersdorf GmbH (1988) also performed a mouse micronucleus test with HC Yellow No. 5. The dye was dissolved in DMSO and delivered by stomach intubation at a dose of 150 mg/kg. Three groups of

five male and five female Crl:NMRI BR mice received a single dose. Animals were killed at 24, 48, and 72 h. A negative-control group received the vehicle only and was killed at 48 h. A positive-control group received cyclophosphamide and was killed at 24 h.

No HC Yellow No. 5 cytotoxic effects were noted. The bone marrow composition and the number of polychromatic erythrocytes in bone marrow samples from treated animals was comparable to controls.

The negative-control group was slightly lower than historical controls in this laboratory and the treatment groups were slightly higher than the negative control, but the difference was not statistically significant. Treatment groups were not different from historical controls. The positive-control yielded the expected results. The conclusion was that HC Yellow No. 5 was not mutagenic in the mouse micronucleus test at 150 mg/kg (Österreichisches Forschungszentrum Seibersdorf GmbH 1988).

CARCINOGENICITY

No information was available on the carcinogenicity of HC Yellow No. 5.

CLINICAL ASSESSMENT OF SAFETY

No clinical data regarding the safety of HC Yellow No. 5 were available.

HAIR DYE EPIDEMIOLOGY

Hair dyes may be broadly grouped into oxidative (permanent) and direct (semipermanent) hair dyes. The oxidative dyes consist of precursors mixed with developers to produce color, whereas direct hair dyes are a preformed color. HC Yellow No. 5 is a direct hair dye.

Although the safety of individual hair dye ingredients is not addressed in epidemiology studies that seek to determine links, if any, between hair dye use and disease, such studies do provide broad information and have been considered by the CIR Expert Panel.

In 1993, an International Agency for Research on Cancer (IARC) working group evaluated 78 epidemiology literature citations and concluded that "personal use of hair colourants cannot be evaluated as to its carcinogenicity" and that "occupation as a hairdresser or barber entails exposures that are probably carcinogenic" (IARC 1993). The IARC report did not distinguish between personal use of oxidative/permanent versus direct hair dyes, or distinguish among the multiple chemical exposures in addition to hair dyes to which a hairdresser or barber might be exposed.

In 2003, an updated review of the available epidemiology literature was prepared (Helzlsouer et al. 2003). This review considered 83 literature citations available since the IARC review. The authors found that hair dye exposure assessment ranged from ever/never use to information on type, color, and duration and frequency of use. The authors found insufficient evidence to support a causal association between personal hair dye use and a variety of tumors and cancers. The review highlighted well-designed studies with an exposure assessment that included hair dye type, color, and frequency or duration of use, which found associations between personal hair dye use and development of bladder cancer, non-Hodgkin's lymphoma, and multiple myeloma. These findings, however, were not consistently observed across studies.

The CIR Expert Panel did specifically note reports from a case-control study (Gago-Dominguez et al. 2001, 2003), which did suggest a possible genetically susceptible subgroup, which detoxifies arylamines to a lower degree than the general population. The study authors hypothesized that this subgroup may be at greater risk of bladder cancer from hair dye exposure. Helzlsouer et al. (2003) noted that these results were based on small sample sizes.

Several studies published since the Helzlsouer et al. (2003) review also have been considered. Discussion of the available hair dye epidemiology data is also available at http://www.cir-safety.org/findings.shtml.

Bladder Cancer. Andrew et al. (2004) reported a case-control study of New Hampshire residents whose bladder cancers were entered into a state registry from 1994 to 1998. A follow-up study by Kelsey et al. (2005) examined the links between those bladder cancer cases with an inactivated tumor suppressor gene (TP53) and various exposures. Huncharek and Kupelnick (2005) performed a meta-analysis of six case-control studies and one cohort study. Takkouche et al. (2005) performed a meta-analysis of the Andrew et al. (2004) study and nine other personal use case-control or cohort studies. Ji et al. (2005) reported a cohort occupational study not included in the above meta-analyses. Lin et al. (2006) presented a case-control study of personal permanent hair dye use. Serretta et al. (2006) reported preliminary results from a multicentric study.

Lymphoma and Leukemia. Rauscher et al. (2004) reported a U.S./Canadian case-contol study of adult acute leukemia. Zhang et al. (2004) and Zheng et al. (2004) examined the relationship of hair dye use or diet with non-Hodgkin's lymphoma in a case-control study in Connecticut. Takkouche et al. (2005) reported a meta-analysis of reports of hematopoietic cancers, including those by Rauscher et al. (2004), Zhang et al. (2004), and 17 other studies. Mester et al. (2005) reviewed 10 epidemiology studies regarding the relationship between occupational exposure in hairdressing and diseases of the malignant lymphoma group. A case-control study in Spain by Benavente et al. (2005) examined the association between lifetime hair dye exposure with various lymphomas, including chronic lymphocytic leukemia.

Other Cancers. Takkouche et al. (2005) included breast cancer and childhood cancers in their meta-analysis. Efird et al. (2005) studied the association between the use of hair-coloring agents the month before or during pregnancy with childhood brain tumors in 1218 cases between 1976 and 1994. Heineman et al. (2005) studied 112 women in Nebraska newly diagnosed with brain cancer (glioma). McCall et al. (2005) reported on the relationship between childhood neuroblastomas and maternal hair dye use in 538 children born between 1992 and 1994 in the U.S. and Canada.

Other Diseases. Park et al. (2005) reported an occupational case-control study of neurodegenerative diseases, including Alzheimer's disease, presenile dementia and motor neuron disease.

In considering this information, the CIR Expert Panel agreed that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other endpoints described in the Helzlsouer et al. (2003) review.

The Panel stated that use of direct hair dyes, although not the focus in all investigations, appears to have little evidence of an association with adverse events as reported in epidemiology studies. However, direct hair dyes are a diverse group of chemicals and the determination of safety may hinge on other safety test data.

The Panel recognizes that hair dye epidemiology studies do not address the safety of individual hair dyes, but is concerned that studies have demonstrated an association between use of oxidative/permanent hair dyes and some cancer endpoints. The Panel, therefore, strongly supports the need to replicate these studies, along with further studies to examine the possibility of susceptible subpopulations. Additional studies examining bladder cancer, non-Hodgkin's lymphoma, and multiple myeloma and hair dye use are underway and it is the intent of the CIR Expert Panel to periodically review hair dye epidemiology studies and update this section.

SUMMARY

HC Yellow No. 5 is a direct hair dye. Hair dyes containing HC Yellow No. 5, as "coal tar" hair dye products, are exempt from the principal adulteration provision and from the color additive provision 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. Such preliminary testing on or by individuals should be done using an open patch test that is evaluated at 48 h after application of the test material.

Absorption of HC Yellow No. 5 through skin is <0.2%.

The oral LD_{50} for rats is 555.56 mg/kg. No significant toxic effects were observed after chronic oral exposure of HC Yellow No. 5 to dogs.

Mild dermal irritation, but no dermal sensitization or ocular irritation were observed in laboratory animals.

Results of fertility and reproductive performance, teratology, and developmental studies were negative.

HC Yellow No. 5 was found to be nonmutagenic and noncytotoxic in standard laboratory assays.

Although the safety of individual hair dye ingredients is not addressed in epidemiology studies that seek to determine links, if any, between hair dye use and disease, such studies do provide broad information and some 78 studies were considered in 1993 by an International Agency for Research on Cancer (IARC) working group. They concluded that "personal use of hair colourants cannot be evaluated as to its carcinogenicity" and that "occupation as a hairdresser or barber entails exposures that are probably carcinogenic." The IARC report did not distinguish between personal use of oxidative/permanent versus direct hair dyes, or distinguish among the multiple chemical exposures in addition to hair dyes to which a hairdresser or barber might be exposed. In 2003, an updated review of the available epidemiology literature was prepared. This review considered 83 literature citations available since the IARC review and concluded that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other endpoints described.

Use of direct hair dyes, although not the focus in all investigations, appears to have little evidence of any association with adverse events as reported in epidemiology studies.

DISCUSSION

The CIR Expert Panel noted that in order to be exempt from the misbranding provisions of the Food, Drug, and Cosmetic Act, a statement cautioning users to test hair dye products on a small area of skin prior to actual use must be displayed on all coal tar hair dye products. Preliminary testing on or by individuals should be done using an open patch test that is evaluated at 48 h after application of the test material, as advised in product labeling. Users, therefore, would be able to determine their individual reactions to hair dye products containing HC Yellow No. 5.

The available safety test data demonstrate that HC Yellow No. 5 does not produce significant irritation or sensitization in animals in maximization tests, suggesting that HC Yellow No. 5 would not produce significant reactions in humans. HC Yellow No. 5 was not found to be toxic in chronic toxicity studies, other dermal irritation and sensitization, ocular irritation, or reproductive and developmental toxicity tests. This suggests an overall low potential for harmful effects. Although there were no data available on the carcinogenic effect of HC Yellow No. 5 and a genotoxicity assay using bacterial cells did indicate an increase in revertants, the Panel noted that in several mammalian cell test systems, HC Yellow No. 5 was not mutagenic. In addition, the concentration of HC Yellow No. 5 in hair dye products is low, the time of skin exposure to these products is short, and skin absorption is appears to be low.

In considering the available hair dye epidemiology data, the CIR Expert Panel concluded that the available epidemiology

studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other endpoints. Direct hair dyes, although not the focus in all investigations, appear to have little evidence of an association with adverse events as reported in epidemiology studies. The Panel recognizes that hair dye epidemiology studies do not address the safety of individual hair dyes. Based on the available data on HC Yellow No. 5, however, the Panel determined that this ingredient would not likely have carcinogenic potential as used in hair dyes.

CONCLUSION

The CIR Expert Panel concluded that HC Yellow No. 5 is safe as a hair dye ingredient in the practices of use and concentration as described in this safety assessment.

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